NON-Q WAVE MYOCARDIAL INFARCTION

GROOTE SCHUUR HOSPITAL

CORONARY CARE UNIT

1990 - 1993

A. OKREGLICKI

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DECLARATION

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ABSTRACT

Non-Q Myocardial Infarction (NQMI) is considered to be an unstable condition with increased risk of recurrent infarction. Thus aggressive approaches in management have been recommended. However, there is no firm evidence that this strategy influences the course of NQMI patients favourably.

To determine the experience at Groote Schuur Hospital all patients admitted to CCU from 1990 to 1993 with NQMI were analysed retrospectively especially with regard to management and outcome. One-hundred and eighty-one patients were admitted with NQMI. Seventy-eight percent (141) remained cardiovascularly stable in the early period after the index event; 51% (93) underwent cardiac catheterisation during that hospital admission and revascularization was performed in 29% (52).

There were 2 deaths during the initial hospital admission, both after surgical revascularisation.

At one year the cardiac mortality was 7%. There were 23 cardiac deaths in all. Early readmission for symptomatic recurrence of ischaemia was identified as a risk factor (p=0.004).

By one year 51% of patients had developed recurrence of symptomatic ischaemia, the majority (62%) in the first 3 months after the primary admission. There was a significantly reduced recurrence in those patients managed actively (i.e. cardiac catheterisation with/without revascularization) as compared to those treated conservatively (p=0.001).

CONCLUSION: NQMI managed in the Groote Schuur Hospital CCU showed low mortality rates (both early and at one year). Retrospective analysis appear to relate active interventional management with a reduction in overall recurrence of symptomatic ischaemia, the majority of which occurred within 3 months of the index NQMI.

ABBREVIATIONS

ACE:	Angiotensin converting enzyme
AMI:	Acute myocardial infarction
CABG:	Coronary artery bypass grafting
CAST:	Cardiac Arrhythmia Suppression Trial
CATH:	Catheterisation (cardiac)
CCF:	Congestive cardiac failure
CCU:	Coronary Care Unit
CHB:	Complete heart block
CMO:	Cardiomyopathy
CPK:	Creatine phosphokinase
CVA:	Cerebrovascular accident (or event)
DM:	Diabetes Mellitus
ECG:	Electrocardiogram
EST:	Exercise stress test
F/U:	Follow-up
GISSI:	Gruppo Italiano per lo Studio...nell Infarto miocardico
GSH:	Groote Schuur Hospital
IABP:	Intra-aortic balloon pump
IHD:	Ischaemic Heart Disease
IRA:	Infarct-related artery
IV:	Intravenous
LAD:	Left anterior descending coronary artery
LV:	Left ventricle
LVEF:	Left ventricular ejection fraction
MB:	MB CPK isoenzyme
MI:	Myocardial infarction
NQMI:	Non-Q wave myocardial infarction
NS:	Non-significant

OM:	Obtuse marginal branch
OR:	Odds Ratio
PMH:	Past medical history
PPAI:	Plasma plasminogen activator inhibitor
PTCA:	Percutaneous transluminal coronary angioplasty
QMI:	Q wave myocardial infarction
RCA:	Right coronary artery
SK:	Streptokinase
TAMI:	Thrombolysis and Angioplasty in Myocardial Infarction Study
TIMI:	Thrombolysis in Myocardial Infarction Studies
TPA:	Tissue plasminogen activator
TVD:	Triple vessel (coronary artery) disease
UAP:	Unstable angina pectoris
WHO:	World Health Organisation

PROLOGUE

NON-Q WAVE MYOCARDIAL INFARCTION IN PERSPECTIVE

Acute myocardial infarction (AMI) is important as a major common cause of death and disability in the Western world. In South Africa, mortality due to ischaemic heart disease (IHD) forms the highest proportion of all death due to natural causes (Figure 1).[1] The majority of these deaths due to IHD are as a result of AMI (51% in 1992).[2]

Statistics from 1985 to 1992 show a decline in mortality rates from IHD in South Africa, in keeping with a world-wide tendency.[3][4] The decline, however, has not been seen amongst Blacks.

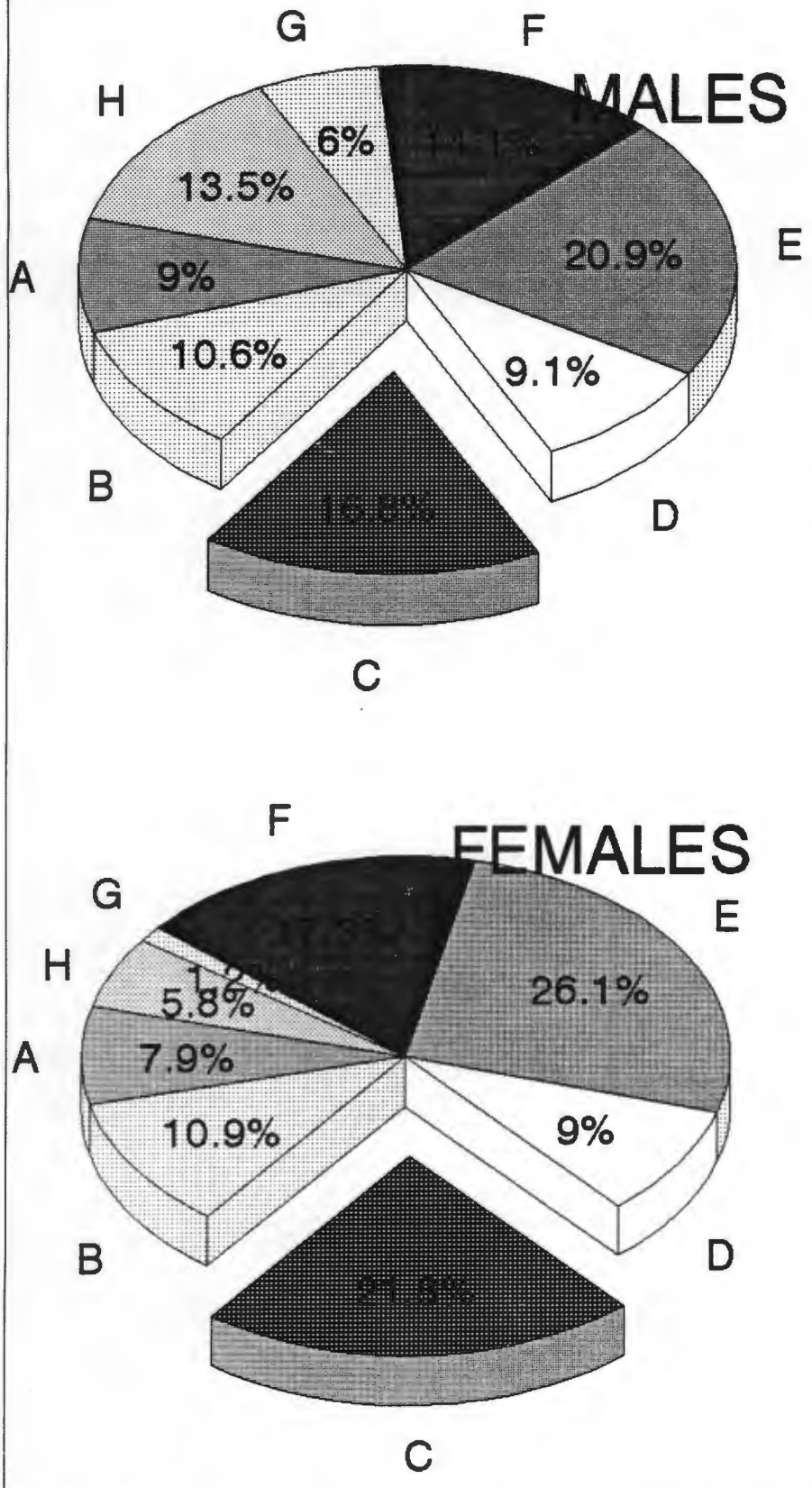
Percentage decline in mortality rates from IHD* 1985-1989[3]:

GROUP**	PERCENTAGE
Asian	11.8%
Black	0%
Coloured	15.0%
White	25.3%

* IHD mortality = sum of ICD codes 410-414 (9th Edition) i.e. AMI, other acute and subacute forms of IHD, old myocardial infarction, angina pectoris, other forms of chronic IHD.

** As from 1991, statistical information regarding recorded deaths is no longer available according to population groups.[2]

SOUTH AFRICAN STATISTICS CAUSES OF DEATH 1992



A: INFECTIOUS/ PARASITIC DISEASES

B: MALIGNANT NEOPLASMS

*C:DISEASES OF CIRCULATORY SYSTEM

D: DISEASES OF RESPIRATORY SYSTEM

E: ILLDEFINED CONDITIONS

F: OTHER NATURAL CAUSES

G: SUICIDE & HOMICIDE

H: OTHER EXTERNAL CAUSES

Figure No.1: Principal causes of death in 1992 in males and females. (Central Statistical Service)[1]

In absolute numbers, over the period 1983 to 1988 there has been a 38.8% increase in the number of reported IHD deaths amongst Blacks.[5][6] This trend probably still persists as it reflects the considerable increases in IHD-risk e.g. hypertension and stress that are known to occur with the process of urbanisation.[7]

Western Cape mortality data shows that IHD ranks first, with 11.8% of all deaths. This is the highest percentage of death in this category for all the provinces.[8]

Non-Q wave myocardial infarction (NQMI) forms about 20-40% of all infarcts.[9][10] Thus, as a major group, NQMI is important and worthy of attention.

INTRODUCTION

INTRODUCTION

This includes a thorough literature review of non-Q myocardial infarction detailing the origin of the term, its value and validity, pathogenesis.

1. TRANSMURAL / NONTRANSMURAL MYOCARDIAL INFARCTIONS

Modern, evidence-based medicine is based on patho-physiological principles. Since the advent of these, attempts have been made to describe or give a sound basis to various observations in every field of medicine.

Likewise with myocardial infarction (MI), an obviously non-uniform or inhomogeneous condition with various causes, presentation and possible lethal outcomes, currently available pathological and physiological tools were used to account and to predict for this observed inhomogeneity. Thus, it is not surprising that the two most solid and objective modes or types of findings then available viz. 1) postmortem/pathological, and 2) electrophysiological data were used in the earlier part of this century and that some link between these two types of data would be made.

Pathology (postmortem studies) showed that MI could be divided into transmural and nontransmural (or subendocardial). This division was strengthened by findings that nontransmural infarcts occurred frequently in severely narrowed, but still patent coronary arteries or resulted from total thrombotic occlusion that had undergone early spontaneous thrombolysis[11][12]. On the other hand, electrocardiographic (ECG) observation noted that some myocardial

infarcts were associated with pathological Q waves and others not. The now discounted incorrect concept of the subendocardium being electrically silent was used as evidence for nontransmural or subendocardial infarcts not displaying Q waves.[13] Thus a link had been made. Numerous studies resulted, all differentiating between transmural and nontransmural MI on the basis of ECG data that did not in fact acurately reflect the pathological facts. Over-reliance and over-interpretation (and perhaps false claims) followed this mistaken belief that the ECG, the most easily reproducible test then available, reflected the anatomy of the myocardial infarct.

2. Q AND NON-Q ≠ TRANSMURAL AND NONTRANSMURAL MI

The term, Q-wave myocardial infarction (QMI) has been used with the implication that Q waves represent through-and-through endocardial to epicardial necrosis. QMI was shown to be associated with larger infarcts and was assumed by some therefore, to be transmural. However, numerous studies show that a poor correlation exists between the extent of necrosis into the thickness of the ventricular wall and the presence or absence of Q waves.[13][14] Despite this, the terms Q wave and non-Q wave myocardial infarction (NQMI), first coined in a letter,[15] were taken up rapidly and preferentially by clinicians and investigators.

Although Q and NQMI are often used to refer to a transmural and nontransmural MI, there is no anatomic evidence to justify this distinction. A correlation study of ECG and pathological findings in 100 cases of Q and NQMI was performed by Antaloczy et al.[16] At autopsy, 55 cases were transmural and 45 subendocardial.

Pathological Q waves appeared in 67% of the cases of transmural infarct and 30% of subendocardial MI. In transmural infarcts, the ratio of QMI to NQMI was 2:1. In subendocardial infarcts just the opposite was observed. Therefore, it is not possible to distinguish with certainty between subendocardial and transmural MI on the basis of the ECG. QMI as 'transmural' and NQMI as 'subendocardial', do not correspond to pathological evidence.

Although it may be inappropriate to assess the validity of ECG findings by means of postmortem anatomy (which represents an extreme stage of Ischaemic Heart Disease (IHD) with old or recent MI), other studies support the view that as markers of transmural extent of infarction, Q waves are neither sensitive nor specific. Furthermore, mapping studies of depolarisation sequences in the human heart show late activation of the lateral and posterobasal walls (<70ms after the earliest ventricular sites of excitation). Thus transmural acute myocardial infarction (AMI) may result in no Q wave genesis owing to the late activation sequence. This was shown in a study, by Landzberg, of 51 patients with total occlusion of the circumflex coronary artery, where only 14 developed Q waves or ECG.[17]

As will be shown in the next section, significant differences exist between QMI and NQMI. It is of little consequence to the physician managing patients, whether the ECG description also accurately defines groups that differ anatomically with regard to the thickness of the injured myocardial wall.[18] Terms such as transmural, nontransmural and subendocardial, should be left to the pathologist. Thus, it has been suggested that the description of

MI based on ECG findings, be confined to what is actually observed on the ECG - i.e., Q wave or non-Q wave MI.[19]

Review of past studies have shown that the differences between what was then called transmural and nontransmural MI are similar to those between Q and NQMI.[20] The criteria for the 2 groups, transmural and nontransmural, closely resemble modern day criteria for Q and NQMI. Thus, many studies on subendocardial MI are extrapolated now to include or be equivalent to NQMI.

3. DIFFERENCES BETWEEN Q AND NON-Q MYOCARDIAL INFARCTION

Since pathological Q waves on ECG are poor markers for transmural myocardial infarction (being neither sensitive nor specific), the usefulness of classification of infarcts by ECG into NQ and Q is therefore dependent on other differences.

Awareness of these differences is important because they determine ultimate management of patients with NQMI who form a not insubstantial proportion of all infarcts (20-40%).[9][10]

Differences between NQMI and QMI are:

A. pre-infarct
B. related to infarct
B. post-infarct

(Apparent discrepancy among results of studies analysing those differences may be related to the inclusion of patients with multiple MI. The occurrences of NQMI as a first cardiac event

differs prognostically from its occurrence as a recurrent cardiac event, as reported by Nicod et al.[21] When assessing differences between NQ and QMI, one must determine whether these refer to first MI and also the methods of enrolling NQMI patients (inclusion criteria) e.g.:

i) all those who do not develop Q waves by discharge; versus

ii) those on presentation who have ECG changes limited to showing ST segment depression or T wave abnormalities.

3A. PRE-INFARCT DIFFERENCES

	QMI	NQMI
Gender		Higher proportion females[22][23][24]
Age	Older	Younger[25][13][26]
Previous MI	Infrequent (22-224%)	Frequent (43-46%)[27][21]
Preceding angina	Less frequent	More frequent[27][29]
Preceding medical conditions		Atrial arrhythmias and cardiac failure more frequent[22][25][21]
Presenting symptoms	Discrete onset	Indiscrete/intermittent onset[30]
Presentation: Circadian rhythm	Present	Absent[31]

3B. INFARCT-RELATED DIFFERENCES BETWEEN NQ AND QMI

	QMI	NQMI
Site	Anterior MI most frequent	Anterior MI less frequent (32)
Serum enzyme CPK	Higher levels	Lower levels (27) Earlier peaks (33)
Infarct size		Smaller (27) (34) (35)
LV function	Impaired frequently	Normal/mildly impaired (if 1st MI) (34) (22)
Biochemistry: TPA PPAI	 Elevated Elevated	 Similarly elevated (36) Low
Histology of	Coagulative necrosis	Contraction band necrosis (35)
ECG	ST segment elevation	ST segment depression (13) (37) ST segment elevation T inversion
Coronary angiography: a) Infarct-related artery b) Collaterals	 Occluded Infrequent	 Patent (33) (38) (39) Frequent (40) (41)

1) **Infarct Site**

The subanalysis of the TIMI II Study, which included only patients with ST segment elevation, showed there were less anterior MI amongst patients with first NQMI, as compared to first QMI ($p<0.01$).[22] This is in contrast to studies including all types of infarcts which suggested that the anterior area seems to be the predilection site of NQMI where it could be localised.[13]

2) **Serum Enzymes - CPK**

In NQMI, the creatine phosphokinase (CPK) levels are lower.[27] Also, peak CPK levels are attained earlier in NQMI:

NQMI (15 hours after the event) versus QMI (27 hours).[33]

This may represent earlier reperfusion and/or greater collateral supply.

3) **Infarct Size**

Based on peak CPK[27] and CPK-MB isoenzyme/body mass index[34], NQMI infarcts appear to be smaller than QMI. In QMI, the volume of necrosis is usually greater than NQMI. The previous assumption that QMI, being larger, was therefore transmural, should be changed. Rather, it should be considered more extensive in any 3-dimensional way. The appearance of Q waves on the ECG is probably dependent on the amount and site of myocardial necrosis. The amount of myocardium destroyed in NQMI is presumably insufficient for abnormal Q waves to evolve.[35]

A smaller area of acute infarction damage is also suggested by lower wall motion abnormality scores.[42]

4) **Left Ventricular Function**

Higher LVEF is seen among patients with NQMI than amongst those with QMI.

For example: NQMI 50.6% versus QMI 43.7% ($p<0.001$)[34]

In the TIMI II Study subanalysis of patients with infarcts pre-discharge resting LVEF was more likely to be normal in the NQMI patients ($p<0.01$).[22]

5) **Biochemical Differences: - TPA and PPAI**

In a study examining the plasma levels of tissue plasminogen activor (TPA) antigen and plasminogen activator inhibitor activity in NQ and QMI patients before thrombolytic therapy, the mean plasma TPA antigen was similarly elevated in both types of infarcts. The mean level of plasma plasminogen activator inhibitor (PPAI) activity was lower in patients with NQMI:

NQMI 7.3IU/ml versus QMI 17.1IU/ml ($p<0.01$)[36]

This may be related to the higher patency rate of infarct related arteries (IRA) in NQMI.

6) **Histology**

Freifeld et al. reported a higher incidence of histologic evidence of prior infarction among patients with a fatal NQMI

than among those with a fatal QMI.[43] Contraction band necrosis, probably reflecting early reperfusion, is typical of NQMI.[35]

7) **ECG**

Initial ECG differences between Q and NQMI exist.[13] Analysis of initial ECGs of 440 patients[37] showed:

	NQMI	QMI	
ST segment elevation	38%	72%	(p<0.001)
T inversion	36%	17%	(p=0.03)

8) **Signal Averaged ECG**

Late potentials noted on signal averaged ECG may adversely affect prognosis following acute MI. Kuchar showed that NQMI was a predictor of loss of these late potentials if they developed post AMI.[44]

9) **Cardiac Catheterisation**

A study showing patients with NQMI to have lower LV end diastolic pressures:

NQMI 11.7 ± 2.7mmHg versus QMI 16.1 ± 5.9mmHg (p<0.02)[18],

is in keeping with the smaller infarct size and better LVEF in NQMI noted previously.

10) Coronary Angiographic Differences Between Q and NQMI

a) Multi-vessel involvement:

Ogawa's study of the clinical and angiographic features of 119 patients with NQMI and 354 with QMI concluded that:

73% of NQMI patients had multiple vessel stenosis on angiography versus 51% of QMI patients. ($p<0.05$) [27]

Other studies have shown equal numbers of diseased vessels in both NQ and QMI patients. [33] [22]

b) Infarct-related artery (IRA) occlusion/patency:

Complete occlusion of IRA varies in studies:

NQMI 19-51% versus QMI 79-80%. [33] [38] [39]

Occlusion rates also increase significantly and progressively with time. Comparison of coronary angiographic findings during the first 6 hours of either NQ or QMI showed complete occlusion of the IRA:

NQMI 11% versus QMI 91% (p0.0001). [40]

Whereas, angiography up to 3 months after the index event showed:

NQMI 23% versus QMI 54% ($p<0.05$). [45]

Thus, even without thrombolysis, there is a high incidence of patent IRA in patients with NQMI. [46]

Analysis of IRA patency after thrombolysis was performed in the TIMI II Study in which patients with ST segment elevation were given TPA. IRA patency (TIMI flow grade 2 or 3) occurred in:

NQMI 88.8% versus QMI 83.8% (p0.002),

and complete IRA reperfusion (TIMI flow grade 3) occurred in:

NQMI 72.2% versus QMI 62.6% ($p<0.01$).[22]

c) Collaterals:

In the angiographic study within 6 hours of either NQ or QMI, collaterals were found in:

NQMI 45% versus QMI 19% ($p=0.06$),

but more significantly residual perfusion of the IRA by either antegrade or collateral flow occurred in:

NQMI 79% versus QMI 26% ($p=0.0001$).[40]

Another study limited to first infarcts showed a significant difference in incidence of collaterals present:

NQMI 47% versus QMI 3% ($p<0.001$).[41]

d) Myocardial jeopardy:

Jeopardised myocardium is defined as normal or mildly hypokinetic wall motion, as identified on ventriculogram, in

segments distal to a coronary artery lesion causing a stenosis of >50%.[10] Ogawa compared the residual myocardial jeopardy in patients symptomatically stable, 6 months after a first QMI or NQMI. Patients with NQMI had a significant increase in frequency of jeopardised myocardium compared to QMI.[47] (The combination of coronary narrowing with retained wall motion may contribute to the increased frequency of re-infarction seen in NQMI.)

e) Stenotic/culprit lesions:

The 6-hour coronary angiographic study showed a lower incidence of thrombus in patients with NQMI:

NQMI 39% versus 91% (p=0.0002).[40]

A study of first MI (32 patients with NQMI and 38 with QMI), who had coronary angiography both before and after MI without interval procedures, showed, in the angiograms done before infarction:[41]

- mean stenosis severity at the site causing future MI:
  NQMI 23% $\pm$ 35 versus QMI 44% $\pm$ 25 (p<0.01)
- eccentric and irregular plaques:
  NQMI 13 % versus QMI 56% (p<0.001)

Review of the pre-infarct angiograms showed that, NQMI patients tended to fall into 2 categories - either minimal or no stenosis (<20%) or else a severe stenosis (>70%).

This study therefore suggested that the atheromatous plaque substrate was different in QMI and NQMI. NQMI occurred typically at a site shown by pre-MI angiography to be usually non-ulcerated and either minimally or severely stenosed before the MI. QMI, by comparison, occurred where stenosis was moderate with plaque eccentricity and ulceration. Such differences may be responsible for differences in thrombus lability and collateral development and consequently in different clinical profiles.[41]

f) Aneurysm formation:

An angiographic study showed that apical aneurysms occurred exclusively in patients with QMI.[48] The association of death due to cardiac rupture and QMI was similar.[27]

11) Thallium/Sestamibi perfusion scans

Fixed thallium perfusion scan defects are less frequent in NQMI:

NQMI 64% versus QMI 98% ($p<0.002$)[18]

indicating that larger areas of myocardium are irreversibly damaged in QMI and perhaps suggesting more reversible ischaemia and remnants of viable myocardium ("incomplete" infarction) in NQMI. (Perfusion defects will be picked up only if a certain critical mass of myocardium is involved. This may not be achieved in NQMI.)

12) **LV remodelling**

The functional impact of LV remodeling during healing after NQ and Q anterior MI has been studied in the dog. NQ wave infarcts were caused by ligating the left anterior descending artery (LAD) and Q infarcts by ligation of the LAD plus collateral obliteration. At 6 weeks, the Q wave group had significantly:

- greater infarct size
- greater transmurality
- more thinning
- greater cavity dilation
- lower global ejection fraction
- higher incidence of aneurysm and LV thrombus.[49]

3C. DIFFERENCES BETWEEN NQ AND QMI RELATED TO THE POST INFARCT PERIOD

	QMI	NQMI
Early mortality	± 20%	± 10% [42] [24]
Late mortality		Equivalent to MI [42] [34] [50] [51]
Sudden death	5%	1% [52] [53]
Recurrence ischaemia	± 20%	± 50% [27] [54] [9] [55]
Re-infarction	± 5	± 20% [42]
Re-hospitalisation	± 22%	± 36% [55]

1) **Survival**

a) Short-term/Immediate Survival, or In-hospital Mortality:

It is generally reported in numerous studies that the immediate mortality rate among patients with NQMI is about half that with QMI.[34][42]

Two meta analyses of in-hospital mortality show a significant difference[42][24]

NQMI 10-12% versus QMI 17-19%

Some studies, however, show no difference.[27][21] For example: A study of a large patient population (n=2024) on the short- and long-term clinical outcome after NQ and QMI showed that in-hospital mortality was only lower in patients older than 70 years.[21] The discrepancies in results may be related to types of infarct patients included. The Framingham Heart Study analysing NQ versus QMI, included first infarcts only. This distinct subset had approximately half the early mortality rates of those with prior MI.[10]

Studies undertaken before the advent of antithrombotic therapy show a significant difference in early mortality between NQMI and QM. However, the TIMI II subanalysis showed no significant difference in deaths at 21 days after TPA in patients who presented with ST segment elevation, whether they developed Q waves or not.[22]

b) Long-term survival/Delayed mortality:

There is general consensus amongst studies that long-term mortality rates in patients with NQMI are similar to those with QMI.[42][34] This has been shown in the placebo arms of large drug studies e.g. the Multicenter Diltiazem Post-Infarct Trial (MDPIT)[50] and the Beta-blocker Heart Attack Trial (BHAT)[51] which provided an opportunity to study the natural history of first NQMI.

This lack of significant difference in long-term survival rates is valid up to 8 years after the index event.[54] Other factors used in subanalysis are e.g. first myocardial infarction,[50] previous IHD, CCF, diabetes mellitus (D.M.) or age >75 years, make no difference to these findings.[25]

Thus, unlike early or in-hospital mortality which is significantly lower in patients with NQMI, subsequent mortality is higher in NQMI patient than in QMI patients, resulting in a 1-year mortality similar in both groups. The initial advantage in NQMI patients is soon lost and long-term prognosis is not related to the development of Q waves.

Maisel et al showed that 1-year mortality rates after reinfarction were significantly higher in the NQMI patients.[56]

2) **Sudden Death**

In the placebo group in the Cardiac Arrhythmia Suppression Trial (CAST), NQMI patients had a significantly lower rate of sudden death and cardiac arrest than QMI patients:

NMQI 1% versus QMI 4.6% (p=0.04)

However, the non-fatal ischaemic events in the placebo group were paralleled by an increase in sudden death in the encainide and flecainide groups: for QMI, the relative risk was 1.7, but for NQMI it was 8.2.[52][53]

3) **Recurrence of ischaemia**

Since Q wave myocardial infarcts are often considered completed infarcts, they should be "curative" of angina pectoris. Ogawa et al showed that post-infarct angina occurred more frequently in patients after NQMI:

NQMI 55% versus QMI 21% ($p<0.05$)[27]

This is in keeping with other studies taking all types of NQMI into account.[54][9][55]

In the selected group of first NQMI and QMI presenting with ST segment elevation and treated with TPA (TIMI II Study), no significant difference in recurrence of ischaemia by 6 weeks was found between the two groups.[22] In comparison, the Framingham Heart Study analysis of long-term prognosis after first infarct with a follow-up of 5.1 ± 4.9 years, showed that NQMI patients had a significantly higher rate of unstable angina pectoris (UAP).[10] In this study, no thrombolytics were used.

4) **Reinfarction**

A review of 5 studies by Montagne et al showed that re-infarction occurred:

NQMI 21% versus QMI 6% ($p<0.05$) [42]

Retrospective pooled data of 14 studies by Gibson et al of NQMI and QMI with one or more prior infarcts showed a similar significant difference.[57] In patients presenting with a first MI, discrepancy exists: the Framingham Heart Study shows that NQMI had a significantly higher rate of reinfarction than QMI. However, when analysed separately by age and sex, differences in reinfarction rates were only noted in men and those under 65 years.[10]

5) **Re-hospitalisation**

Gibson et al, in the prospective evaluation of 241 patients with NQMI and QMI, noted a higher rate of re-hospitalisation in the former:

NQMI 36% versus QMI 22% ($p=0.034$),

during 27 months of follow-up. The NQMI group also had a greater likelihood of subsequent bypass surgery or angioplasty ($p=0.018$).[55]

6. **Exercise Stress Testing/Ambulatory ECG Monitoring**

A study by Mickly et al, assessing residual ischaemia in patients with first NQ or QMI by means of exercise stress testing (EST) and ambulatory ST segment monitoring, showed

that during early post-discharge daily activities, there was only a trend towards more patients with NQMI demonstrating transient episodes of ST segment depression. However, ischaemic episodes were significantly longer ($p<0.001$) and ischaemic thresholds significantly lower in NQMI ($p<0.0$).[58] Another study showed that objective evidence of exercise induced ischaemia was seen more commonly in NQMI patients:

NQMI 68% versus QMI 32% ($p<0.01$).[18]

Despite the EST, in the study by Mickley et at, significantly predicting development of future angina pectoris,[58] long-term infarct-free survival has been shown to be similar in both NQMI and QMI patients where results are positive,[59] as re-infarction is probably related more to the presence and severity of coronary artery disease than to the presence or absence of Q waves.

7) **Arrhythmias**

Although an 8-year observational study revealed that arrhythmias in general were more frequent in patients after NQMI than after QMI,[60] late ventricular arrhythmias were not, as reported elsewhere.[18] The Worcester Study showed conclusively that NQMI patients had a lower complication rate in the acute phase with less hypotension, ventricular tachycardia, ventricular fibrillation and cardiac arrest.[54]

8) **Clinical Course**

Stone et al studied 471 patients with first infarcts and found that patients with QMI had a worse in-hospital course compared

with NQMI patients, with more cardiac failure (paralleling the lower LV ejection fraction and larger infarct size).[34] This lower rate of cardiac failure in NQMI patients persists into late follow-up.[27][10]

Gilpin showed in a large population of patients (n=3665) with all types of acute MI followed up for 1 year that non-fatal recurrence of infarction occurred more often if there was a history of previous MI, cardiac failure, diabetes mellitus, previous angina and a NQMI as index MI, as compared to the infarct-free survivors.[61]

Other clinical factors may influence the outcome. In elderly patients (>70 years), QMI is associated with more in-hospital complications including death, when compared to NQMI ($p<0.05$), but post-discharge mortality is higher in elderly patients with NQMI so that mortality is similar in the 2 groups at 1 year.[26]

9) **Secondary Prevention**

Numerous drug trials with beta-blockers and calcium antagonists have shown different benefits in NQMI as opposed to QMI (see section on Management).

Thus, differences between NQMI and QMI have been related to:

A. Pre-infarct:
- gender
- age
- previous IHD/angina
- presentation

B. Infarct:
- site
- size
- enzymes and other biochemical parameters
- histology and pathogenesis
- ECG
- angiography

C. Post-infarct:
- prognosis (early survival)
- recurrence of ischaemia
- reinfarction
- re-hospitalisation
- exercise stress testing
- clinical parameters and course
- secondary prevention

Most differences in biological and clinical variables between the two types of acute infarction can be related to 3 factors found in NQMI[42][62]:

1. smaller infarct size possibly due to early reperfusion as a result of spontaneous thrombolysis, relief of spasm or both;
2. more frequent patency of infarct-related arteries;
3. a larger residual mass of viable, but jeopardised myocardium within the perfusion zone of the infarct-related artery, in part due to a better collateral supply.

Thus, NQMI appears to be a relatively unstable condition with lower initial mortality and a higher risk of later infarction. These cancel each other out so that by 3 years, or even earlier, mortality rates in NQ and QMI are equal.[19]

The challenge for clinicians is to utilise the early window of opportunity to identify patients with NQMI at risk of subsequent events and to intervene in an attempt to prevent the mortality "catch up".

4. INVALID: DIFFERENCE BETWEEN NQ AND QMI

The ECG dichotomisation of infarction into Q and NQMI is not universally favoured. Moss feels that it is an oversimplification of a complex disease process with limited prognostic and therapeutic utility. The categorisation does not provide sufficient sensitivity, specificity or predictive accuracy about the subsequent clinical cause of patients with first myocardial infarct, to use as reliable data.[63]

The terms 'QMI' or 'NQMI' have even been criticised as representing a "halfway house of the intellect", since the presence or absence of Q waves accompanying MI does not delineate or differentiate any pathological or clinical subset.[64]

The dichotomy of Q versus non-Q may have produced unwarranted lumping of the large number of ECG permutations and combinations of wave-form that occur over time, unrelated to the presence of Q waves.[65] Nor are these categories absolutely distinct or defined. Some patients with acute ST segment elevation will

rapidly develop Q waves; others will evolve Q waves over days, and others will never develop them.[66] Therefore, the admission ECG, for purpose of classification, is unreliable. It may therefore be more appropriate to regard acute MI as "electrocardiographically undifferentiated"[35] during the first several hours after the index event, until enough time (24-48 hours) is given for the ECG to evolve. ST segment shifts are unreliable predictors of subsequent Q development after infarction. The 12-lead ECG is restrictive and misses Q waves. It has been shown that Q waves may be inconsistent, even over relatively short periods of time, e.g. during a particular phase of respiration.[65]

The ECG is also too blunt an instrument to differentiate, with precision, the state of reperfusion after thrombolysis. The ECG is not helpful in identifying patients with initially incomplete coronary occlusion who may not require thrombolysis. Although the ECG can demonstrate successful reperfusion when applied to large groups of patients, the value in the individual patient is minimal.[35]

What about the differences attributed to Q and NQMI? Spodick noting numerous similarities between these two groups, warned that these terms are inadequate for clinicopathological and prognostic classification of acute MI.[67] Fox, in comparing prognosis of NQ and QMI, showed that at one year the mortality, reinfarction and angina rates were similar in the two groups and on this basis suggested that the distinctions between them need not influence management decisions.[45] This argument is flawed as the equivalent long-term prognosis is due to the catch-up of events in NQMI.

Thus, the similarities between QMI and NQMI are:[14][25][45]

1. Both may be pathologically transmural or not
2. Number of diseased coronary vessels
3. Grade of coronary artery stenosis
4. Long-term reinfarction
5. Long-term mortality.

Taking into account that any binary classification system may fail to take into account the heterogeneous manifestations of acute MI, and may result in oversimplification, the balance of the evidence still suggests that, provided one is aware of the shortcomings in ECG classification and the possible heterogeneity of NQMI in particular, significant differences do exist between NQMI and QMI, especially at the time of infarctions and in the early period thereafter.

5. NQMI - A HETEROGENEOUS GROUP

That NQMI is a non-uniform group has already been alluded to. This refers not only to classification, but also to mechanism, inclusion criteria and prognostic implications. At present, Q wave MI forms about 60-80% of all infarcts,[13][9][10] and the rest, by definition, may be described as being non-Q.

Studies, eg TIMI IIIB in UAP and NQMI have restricted inclusion to patients only with ST segment depression.[68] ST segment elevation

during the early hours of evolving infarction however, is not an invariable harbinger of subsequent Q development[69].

Natural history studies of patients with acute MI who present only with ST segment elevation have shown that up to 37% will subsequently develop a NQMI.[46] A study has shown that ST segment elevation <2mm on admission is an independent predictor of subsequent development of NQMI, whereas only 26% of patients with >2mm ST segment elevation on admission developed NQMI.[28] It is generally believed (but not very well substantiated), that if acute myocardial infarction presents with ST segment elevation and Q waves have not developed, this may be considered to mean some salvage of myocardium has been achieved. These are the aborted Q wave infarcts.

The NQ infarcts with ST segment depression and T inversion are also non-uniform. In a study[70] on the different clinical implications for ST depression and T inversion in NQMI patients, ST elevation was shown to precede T wave inversion in the same leads in 80% of the T 'group'. Marked differences in cardiac status were noted:

Cardiac Status	**ST ↓ (n=22)**	**T ↓ (n=20)**
Killip Class II-IV	59%	20% ($p<0.5$)
1 month mortality	41%	0% ($p<0.05$)
No. of coronaries diseased	multiple	single

T wave inversion thus implied recovery phase of infarction within a presumed one-vessel territory. ST segment depression suggested

extensive ischaemia in the subendocardium of multi-vessel territory. Another study analysing ST segment deviation in two or more leads on the admission ECG of NQMI patients showed a positive predictive value of 79% for recurrence of ischaemia or myocardial infarction within three months and a negative predictive value of 64%.[71]

Features of incomplete infarction are shared by NQMI and reperfused acute myocardial infarction after thrombolysis:[35]

- subtotal coronary occlusion
- early CPK wash-out
- preservation of global and regional LV function
- high incidence of reinfarction and post-infarct angina
- high incidence of residual myocardial ischaemia during non-invasive testing.

The incidence of the so-called NQMI after successful reperfusion with thrombolysis (± 40-45%)[35][28] appears to increase the number of aborted QMI which are expected to occur by means of spontaneous natural thrombolysis to occur in some patients presenting with ST elevation.[46]

Acute MI with R wave regression is distinct from acute QMI as shown by clinical features in keeping with typical NQMI (lower CPK, lower incidence of cardiac failure and in-hospital mortality) and angiographic features of a higher rate of spontaneous opening of infarct-related arteries within 48 hours.[72]

Patients presenting with acute MI and left bundle branch block (LBBB) on ECG, strictly speaking, may be lumped into the NQMI group. They should be considered an indeterminate type of acute MI.[26]

Using various ECG definitions for MI (Minnesota Code, WHO Code, etc.), the concept of NQ posterior MI does not exist because it is characterised by indirect "mirror" signs. However, routine recording of leads V_8 and V_9 has shown that this entity of NQ posterior MI exists.[13] The fact that the anterior area seems to be the predilection site of NQMI may be partly due to the general recognition only of the Q wave variant of posterior MI (i.e. R/S ratio >1 in V_1 - V_2).

Electrocardiographically silent infarcts occur. Lateral and basolateral MI in particular, may be silent, even if they are transmural as shown by postmortem studies.[17]

As a result of all these variables, no set of defining criteria for Q and NQMI is used in trials:

1) **Variable times of ECG categorisation:**
   - most studies perform this at hospital discharge;
   - in the TIMI II Study, this was based on the Day 2 ECG (since it was considered the time that most physicians made a decision regarding catheterisation in stable patients).[22] Eisenberg et al, showed that only 1.5% of patients with NQMI after thrombolysis progressed to QMI in the period after 24 hours to hospital discharge.[73];
   - in TIMI IIIB this was based on the admission ECG[68];

- to confound the issue, a study of NQMI only showed that in 55%, transient Q waves occurred.[70]

2) **Variable interpretations of ECG:**

- some NQMI studies include all those that do not develop Q waves and others only those with ST segment depression or T changes on the admission ECG;
- some use specific criteria which may not be generally acceptable e.g. the Multicenter Post-Infarction Program code calls any anterior infarct a NQMI if there are no Q waves and only ST/T changes, yet the loss of R wave amplitude in V_5 and V_6 is regarded as Q wave equivalent infarction.[74]

It is thus quite obvious that ECG changes in NQMI are not specific for this entity. They are also found in subendocardial ischaemia, rapid heart rates, electrolyte abnormalities, intraventricular conduction abnormalities and with certain medications (e.g. digoxin). Unlike QMI which is likely to arise in a patient presenting with ST segment elevation, and acute management can be based on ECG with relative certainty, NQMI may occur in a variety of ECG's which are non-specific and may be associated with other abnormalities. Perhaps there is a place for quick, early enzyme analysis if it is shown that acute management would play a role in changing the acute outcomes for various subcategories of the acute coronary syndrome.

3) **Variable enzyme criteria**

The definition for CPK-enzyme rise to secure a diagnosis of NQMI also varies. Most studies require this to be twice the upper normal value for their laboratory according to the WHO definition for AMI. However, some, for example, the widely quoted cross-sectional analysis of coronary angiographic findings soon after NQMI by De Wood et al, included those patients with CPK 150% of their top laboratory normal value before intervention.[75] With the availability of very sensitive myocardial enzyme detection techniques, previously categorised anginal episodes are now being diagnosed as enzyme positive NQMI.[63] The problem with their inclusion is that mild CPK-MB increases have also been detected in 20% of patients within 24 hours after successful PTCA.[76] CPK may be released into coronary blood by transient, severe ischaemia without associated cellular myocardial necrosis.[77]

Thus, the heterogeneous NQ group of myocardial infarcts includes:

1) Subendocardial infarction with transient ST-T changes
2) Intramural infarctions with giant negative T waves[63]
3) True NQ posterior infarcts
4) Silent infarcts (may include transmural posterior, lateral or basolateral MI)
5) Aborted or incomplete infarctions; due to:
   - coronary spasm
   - intrinsic thrombolysis
   - extrinsic thrombolysis
   - angioplasty

6) Variably interpreted infarcts (by ECG) e.g. "pathological R" infarcts.

6. SIMILARITIES BETWEEN NQMI AND UAP

There is considerable overlap in literature between unstable angina pectoris (UAP) and NQMI, both falling under acute myocardial ischaemia rather than myocardial infarction. Frequently, for purposes of study, NQMI and UAP are lumped together as "unstable coronary artery disease" or "acute coronary syndrome", e.g. the aspirin study in unstable coronary artery disease;[78] the platelet receptor blocker (GPIIB/IIA) trials.[79][80]

There appears to be some justification for this:

1) Some studies have shown small areas of micro-infarction (without evolution of an ECG infarct) in some cases of UAP. These variants of UAP, with early washout of CPK-MB, represent a link to NQMI.[77] This has prompted trials assessing the use of thrombolytics in UAP (e.g.TIMI IIIB[68]).

2) If one extends the role of the obstructive atherosclerotic plaque to include a dynamic component to explain the unstable state, the classification of unstable angina can indeed be extended to include groups of patients recognised at high risk of subsequent infarction, i.e. patients with NQMI and those with early post-infarction ischaemia. Recognised dynamic components are: rapid progression of disease, active vasomotion, plaque fissuring and thrombus formation with activation of platelets.[81]

3) Evidence from studies:

In a study of 911 patients with NQMI and UAP looking for risk stratification factors, cardiac enzyme levels had no predictive value.[82] Clinical morphological comparison of the infarct-related artery of NQMI and stenotic lesions in UAP have shown similar eccentric atherosclerotic lesions.[83] Reversible defects on Thallium perfusion scanning are characteristic of both UAP and NQMI.

7. DISSIMILARITIES BETWEEN NQMI AND UAP

There is difficulty in interpreting management recommendations of trials that consider NQMI and UAP together, because although the aetiology of these two syndromes appears to be similar, the clinical course and prognosis are quite distinct, with NQMI patients having a higher rate of death and subsequent infarction than patients with UAP.[84][85]

In the TIMI IIIB Study, NQMI patients had a 70% higher risk of death or subsequent MI by 6 weeks:

NQMI 8.6% versus UAP 5.0% ($p=0.05$)[68]

Cohen et al observed that risk of death or subsequent MI by 12 weeks was similarly significant:

NQMI 16% versus UAP 7% ($p=0.01$)[84]

Within the spectrum of conditions caused by ischaemic heart disease, NQMI is found near the middle (Figure No. 2). At the time

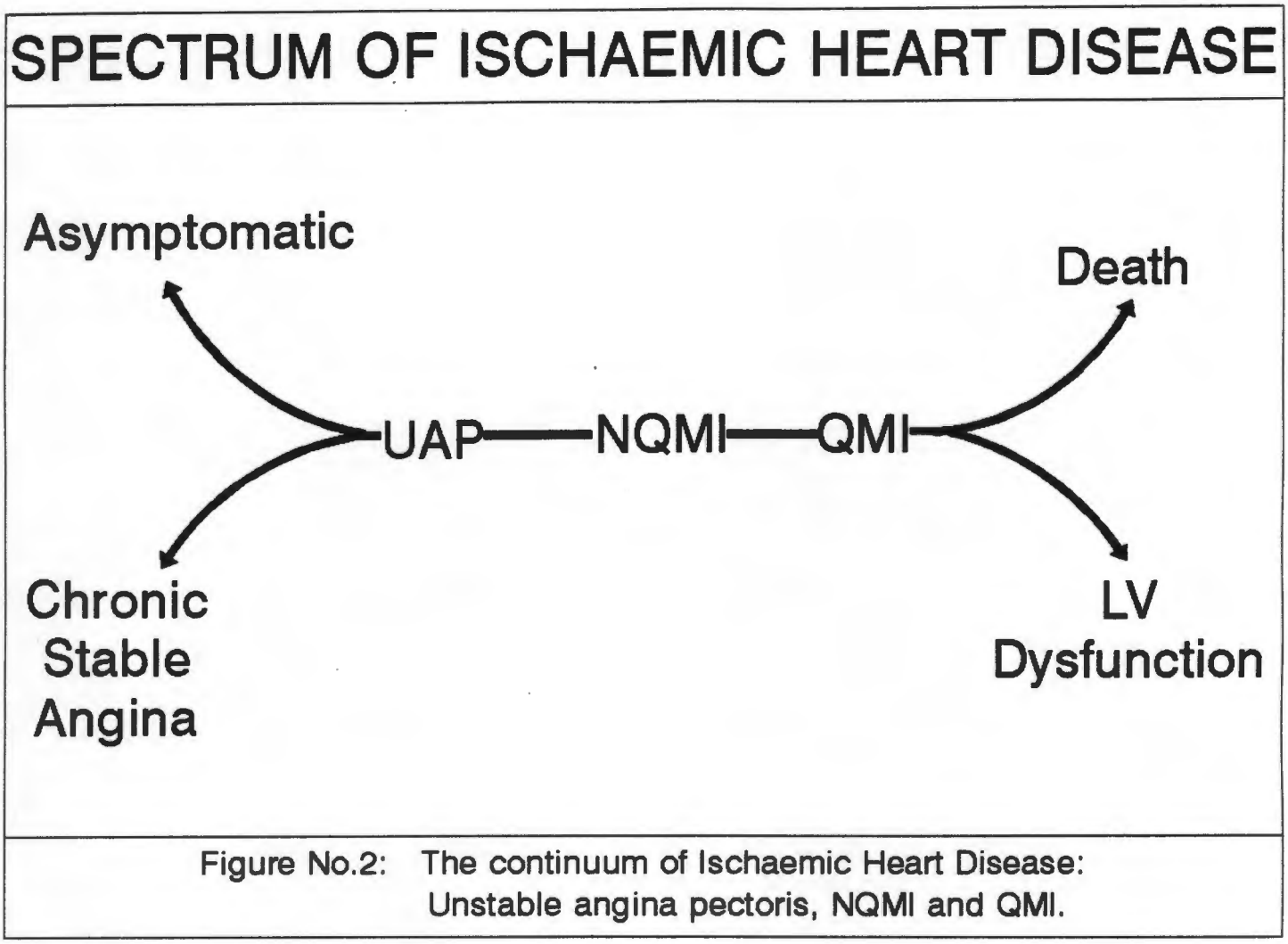


Figure No.2: The continuum of Ischaemic Heart Disease: Unstable angina pectoris, NQMI and QMI.

of MI and early thereafter, NQMI is closely related to UAP (in fact, they usually cannot be differentiated at the time of presentation[83]). Yet, later (in the post-hospital discharge phase) NQMI is more like QMI with similar mortality and long-term outcome.

8. PATHOGENESIS / MECHANISMS INVOLVED IN NQMI

It is important to consider the pathogenetic mechanisms specific for NQMI in order to understand why it remains an unstable condition (more so than in QMI) and where potential strategies of management are possible) (Figure No. 3).

A. PERI-INFARCT

B. POST-INFARCT COURSE

MECHANISMS IN THE SPECTRUM OF ISCHAEMIC HEART DISEASE

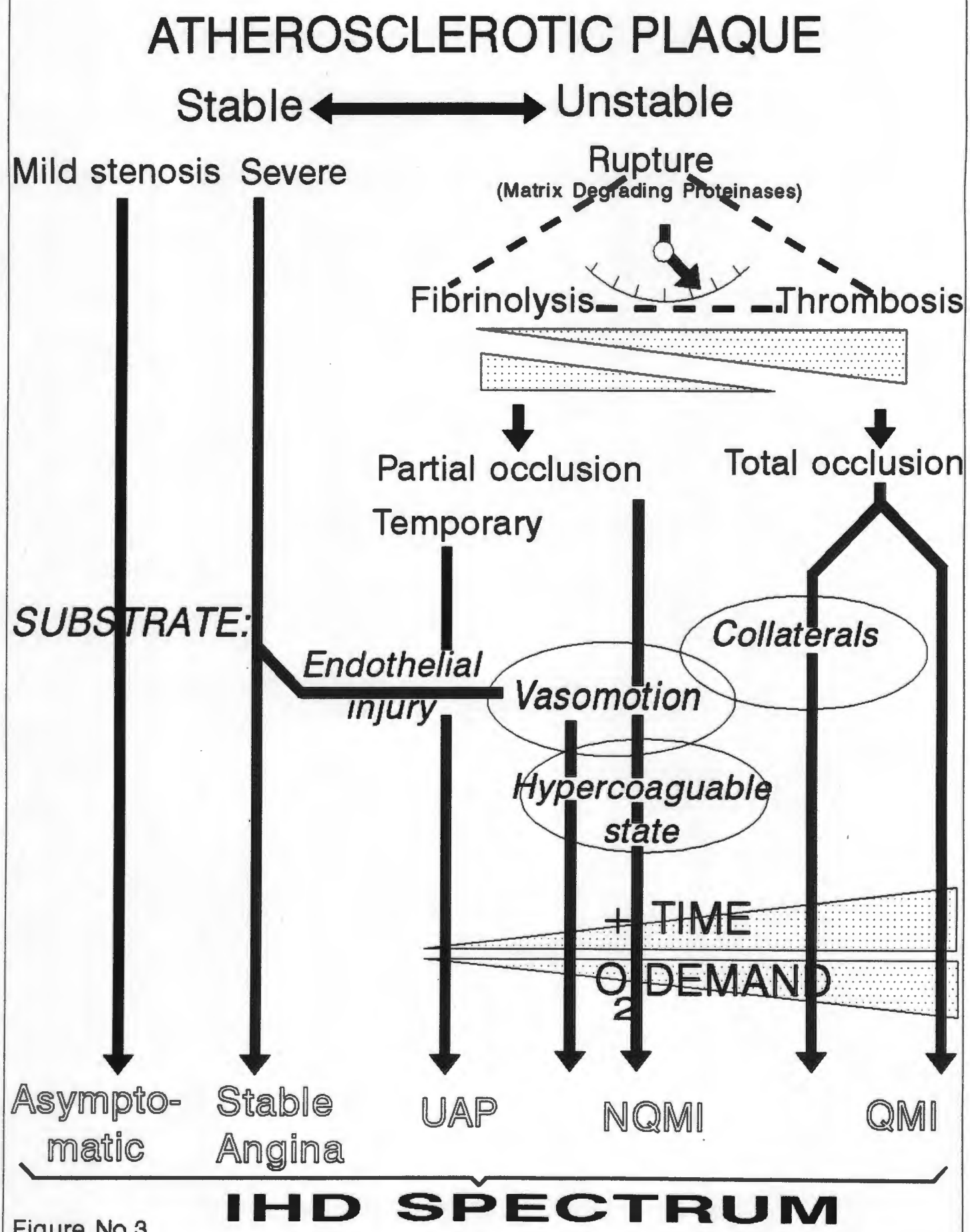


Figure No.3

8A. PERI-INFARCT

NQMI, as in common with other manifestations of the acute coronary syndrome, e.g. UAP or QMI, frequently appears to be triggered by rupture of an unstable atherosclerotic plaque in a coronary artery. This itself is the result of complex inflammatory changes[86] that occur in the plaque which precipitate loss of integrity of the extracellular matrix of the plaque fibrotic cap.[87] The outcome of plaque rupture is dependent on an interacting triad of thrombosis, fibrinolysis and matrix degrading proteinase. The result of this is varying severity of occlusion (partial to total) of variable duration, the effect of which is modified by the myocardial oxygen demand and particularly by the underlying substrate. This may be dynamic, e.g. vasomotion or structural, e.g. collaterals. The final outcome is the spectrum of acute coronary disease.

What is the evidence? A high proportion of NQMI on histological examination has contraction band necrosis, a pattern highly suggestive of transient decrease in perfusion or non-perfusion followed by reperfusion or of reperfusion via well developed collaterals, i.e. a reperfusion injury.[13] NQMI have long been considered to represent aborted QMI with an incomplete necrotic event and a variable degree of sub-epicardial salvage. Non-sustained coronary occlusion may be due to two proposed mechanisms:[35]

1. Early spontaneous reperfusion of a total thrombotic coronary occlusion resulting in an 'altered reflow' phenomenon.

2. Presence of focal vasospasm superimposed on a severely stenotic infarct related artery which abates abruptly resulting in partial restoration of antegrade flow.

The degree to which each contributes remains unresolved. In all probability elements of both mechanisms occur. A transient reduction in coronary blood flow without a permanent and completely obstructing coronary thrombus is probably perpetuated by the underlying substrate, causing vasoconstriction. Endothelial injury at the site of coronary stenosis is associated with platelet aggregation and release of platelet-derived mediators (thromboxane A_2, serotonin) which cause further platelet aggregation and dynamic increases in coronary vascular resistance and reduction in coronary blood flow. White blood cells, and mast cell infiltration of the injured endothelial region, release other mediators (platelet-derived growth factor, platelet activating factor, prostaglandin D_2, endothelin).[88] This sequence causes further platelet aggregation. The small micro-aggregates and platelets, which are beneath the resolution of coronary angiography, are washed downstream[75] and may interact with other mechanisms of reduced flow: abnormal vasomotion (See Figure No. 4). Thus the occurrence of NQMI in multi-vessel coronary artery disease with severe stenoses can be tied in, since dynamic vasoconstriction may be exaggerated if the distal coronary artery has diseased endothelium which has less ability to vasodilate (because of low concentration of endothelial-derived relaxing factor, tissue plasminogen activator and/or prostacyclin).

These mechanisms with the addition of the time variable may thus be responsible for the continuum of the acute ischaemic spectrum:

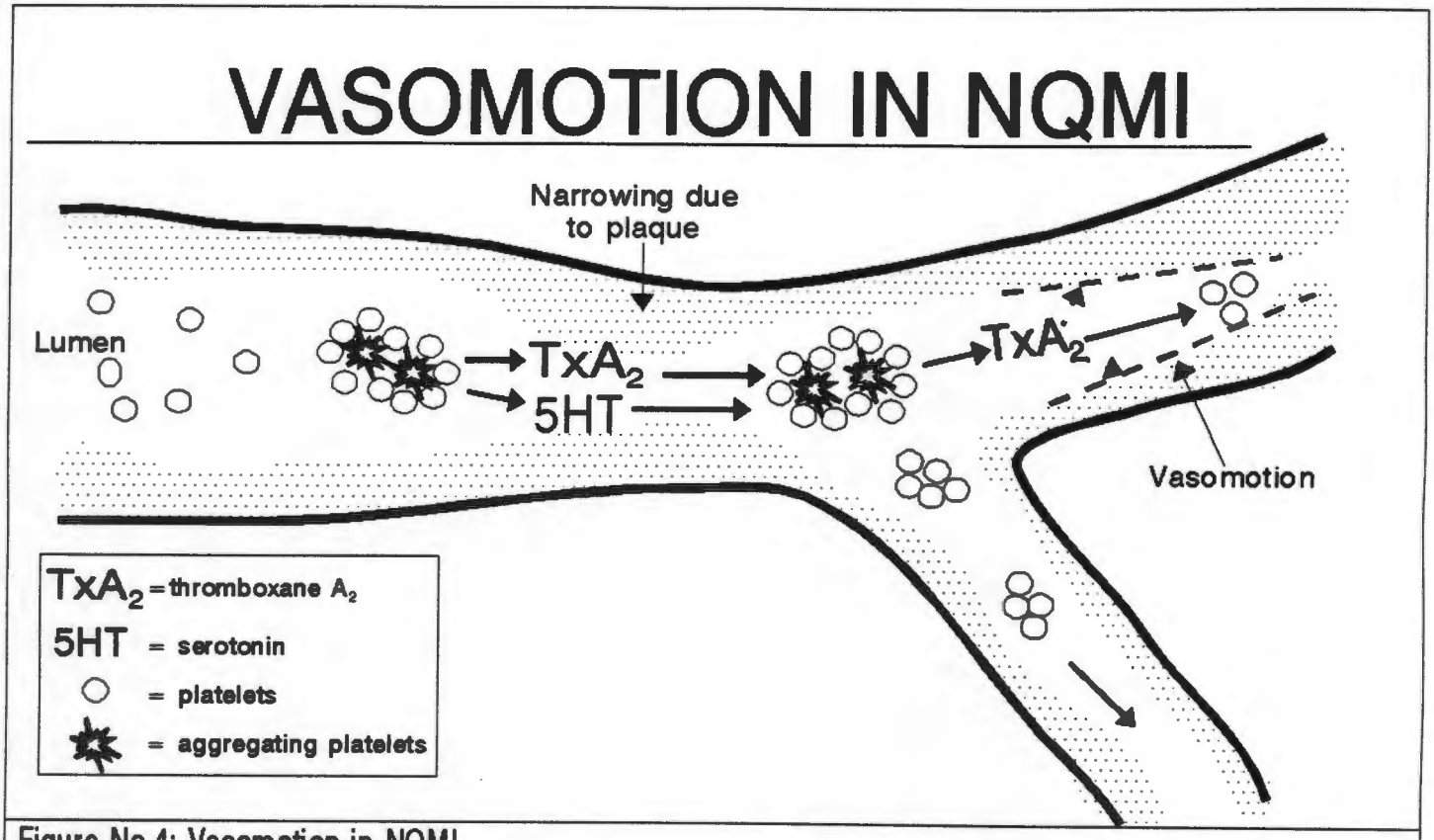


Figure No.4: Vasomotion in NQMI.
A schematic diagram of the possible mechanisms by which aggregating platelets release thromboxane A_2 and serotonin, at the site of luminal narrowing, which cause further platelet aggregation downstream and dynamic reductions in coronary luminal diameter.[88]

- UAP: short spans of severe ischaemia, but no (or only very limited) focal myocardial necrosis
- NQMI: pathophysiological processes causing ischaemia to reduce coronary blood flow for periods of 20 minutes to 2 hours
- QMI: critical reduction of coronary blood flow >2 hours.

Other variables in substrate also play a role:

a) Collaterals:

Studies have shown that patients with prior coronary stenosis ≥70% had a lower prevalence of NQMI, possibly due to chronic

stenoses less likely having plaque rupture and the more frequent development of collaterals.[39]

If NQMI does occur in severe coronary stenosis, it is associated with collaterals. Rentrop et al have shown that sudden coronary occlusion in patients with severe coronary stenosis causes the collateral channel filling to improve rapidly, (within $1\text{-}1^{1}/_{2}$ minutes).[89] Thus, partial perfusion is still possible with limitation of infarct size.

b) Major complications of rotational atherectomy include infarction. NQMI occurs in approximately 3.8% of patients and is significantly associated with the female gender and a history of previous MI.[90] It appears that it is not only the mechanism or the pathological process, but also the underlying substrate that is responsible for NQMI.

The complex dynamic interaction of plaque, thrombosis and collateral supply that results in NQMI[42] indicates sites of possible therapeutic intervention: e.g. antithrombotic agents, antiplatelet agents, inhibitors of platelet aggregation, antiserotonin agents, endothelium-derived relaxing factor promoters, anti-inflammatory agents and matrix proteinase inhibitors (that may render atherosclerotic plaques more stable),[87] etc.

Other mechanisms of NQMI:

- severe increase in myocardial oxygen demand;
- severe generalised impairment of coronary perfusion.

8B. POST-INFARCT COURSE

Mechanisms involved in the unstable post-infarct course of NQMI are essentially a perpetuation of those involved in the acute infarction. It is well-known that reinfarction and angina are more frequent after NQMI. The post-infarct instability may be due to:[13][91]

1) peri-infarct residual ischaemia;
2) sustained by high grade stenosis;
3) inadequate collateral circulation with the supervening of additional pathophysiological events;[92]
4) progressive stenosis in the infarct-related artery;
5) further coronary thrombosis;
6) platelet aggregation;
7) coronary vasospasm.

The dynamic component of the atherosclerotic plaque may be responsible for the unstable state.[81] This is in keeping with the findings that early reinfarction (within 6 months) has been shown to occur in the same ECG region in which initial infarction had occurred.[93] (Late infarction is randomly distributed.)

Some evolution does occur after the index NQMI. Total coronary occlusion of the infarct-related artery is infrequently observed (26%) in the early hours of NQMI, but increases moderately in frequency (42%) over the next several days. This is paralleled by an increase in the presence of visible collateral vessels.[75]

In addition, it appears that activated substrate (including lesion hyperactivity) requires some time to return to baseline. The only

significant predictor of clinical restenosis after percutaneous transluminal coronary angioplasty (PTCA) following NQMI, is the interval duration between myocardial infarction and the PTCA. In a study assessing the usefulness of PTCA after NQMI, the interval among patients with recurrence of symptoms was 4 to 5 weeks and among those without recurrence 12 to 18 weeks ($p<0.04$).[92] Furthermore, in patients with unstable angina, intracoronary thrombus formation is associated with a hypercoagulable state as shown by elevated levels of thrombin-antithrombin III (TAT) complexes and fibrin degradation products.[94][95] The persistence of this state, together with disturbed fibrinolysis, may increase the risk for further coronary events.

9. MANAGEMENT RECOMMENDATIONS

Should the subset of patients with NQMI be treated any differently to other infarct patients?

The minimal rise in CPK, absence of cardiac failure or shock, may lull one into believing that NQMI is benign. However, the conclusions from NQMI versus QMI studies must be taken into account.

1. NQMI is generally accepted to represent an aborted QMI resulting in an 'incomplete' necrotic event. It is thus believed that:

   - there are areas still at risk of further ischaemia
   - salvage of still viable myocardium is possible.

2. NQMI is believed to be a relatively unstable condition with increased risk of recurrent infarction (NQMI may constitute the highest risk subset of post-infarct patients.[96]).

3. Extensive damage from recurrent myocardial necrosis has a considerable deleterious effect on long-term survival.[97]

Therefore, patients with NQMI would be expected to benefit from prophylactic treatment that prevents reinfarction (possibly even more than patients with QMI).

9A. MEDICAL

In addition to the generally applied principles of medical management of patients with manifestations of the acute coronary syndrome, the following need to be considered:

1) General Measures
2) Antithrombotic therapy
   Aspirin
   Antiplatelet therapy
3) Beta-blockers
4) Calcium antagonists
5) ACE-inhibitors

1) General Measures

Firstly, because of the high incidence of early recurrence, NQMI patients may merit intense and prolong monitoring for detection of ECG changes and enzyme elevation. Greater awareness of recurrence of ischaemia and need for management must be encouraged. This increased vigilance is required not

only for the initial period of hospitalisation. Patients with NQMI pass through a highly vulnerable period for the first 6-12 weeks after the index event and the propensity for further complications probably extends throughout most of the first year after the infarct.[83]

2) **Antithrombotic / Antiplatelet Therapy**

A combination of antithrombotic therapy (heparin, warfarin) with aspirin in UAP and NQMI has shown a significant reduction in recurrent ischaemic events by 14 days.[98] The Persantin-Aspirin Reinfarction Study (PARIS-2) showed a 48% reduction in cumulative incidence of coronary events (mortality and reinfarction) in patients with NQMI who received active treatment.[99] Low dose aspirin, 75mg/d, has been shown by the RISC group in a prospective trial of 796 men with unstable coronary disease (UAP and NQMI) to reduce the risk of MI and death and severity of angina by 3 months.[78] This was most significant with the NQMI group of patients ($p<0.0001$).[100] The risk reduction was maintained at one year.[78] This group found no protective effect of intravenous (IV) heparin alone against recurrence of MI. On the other hand the combination of IV heparin and aspirin was the only regimen that significantly reduced the risk of MI during the first 5 days in hospital.[100]

Other treatment strategies with newer platelet inhibitors (e.g. GPIIb/IIIa inhibitors[79][80]) and antithrombotic agents (e.g. direct thrombin inhibitors such as hirudin) i.e. substances more effective than the combination of heparin and aspirin in inhibiting rethrombosis while endogenous

fibrinolysis occurs may be useful, provided NQMI can be identified more accurately.[39]

3) **Beta-Blockers**

As there are multiple differences between Q and NQMI it is not illogical to assume that secondary prophylaxis post MI could also differ. Gheorghiade et al observed no benefit of propranolol among the 601 patients with NQMI in the beta-blocker Heart Attack Trial (BHAT).[101] It has therefore been hypothesized that beta-blockers are ineffective in NQMI patients.[102][103]

Yusuf argues that this hypothesis of beta-blockers' ineffectiveness is likely to be spurious because the statistical power of sub-group analysis in the BHAT Study was poor.[104] Furthermore, the results are directly contradicted by the Norwegian Timolol Trial. This trial showed that timolol showed a significant decrease in mortality among those with NQMI (14% in the placebo group versus 7% among treated patients).[105][106] No significant reduction in reinfarction in NQMI patients was noted. Therefore, with all available information and recognising the limitations of sub-group analysis, Yusuf suggests that beta-blockers are likely to benefit patients with NQMI. The size of the benefit is not clear, but may be close to a 25% decrease in mortality and reinfarction.

4) Calcium Antagonists

a) Early Use

Evidence exists that NQMI patients are prone to reinfarction in the same area as the original injury i.e. after a NQMI there remains viable, but jeopardised myocardium within the perfusion zone of the infarct-related artery (IRA).[24] Prophylactic therapy aimed at this IRA may protect this highly vulnerable tissue from further ischaemic insults. Vasospasm has been shown to be an important component of the pathogenesis of the acute event and perpetuation of the ischaemia. In addition, since angiographic findings (as shown by De Wood et al) support the concept of progression to total occlusion, short-term therapies aimed at maintaining antegrade blood flow may help.[75] This may justify the attempted use of calcium antagonists (calcium channel blockers) for their vasodilatory or anti-vasospastic actions.

A double-blind randomised study (the Diltiazem Reinfarction Study, DRS) (90mg 6 hourly) on reinfarction after a NQMI starting treatment within 72 hours after the infarct and continuing for 14 days, showed 51.2% reduction in reinfarction ($p=0.03$) and a 49.7% reduction in frequency of refractory post-infarct angina ($p=0.04$). However, 2-week mortality was unchanged. This study therefore concluded that diltiazem was effective in the prevention of early reinfarction and of severe angina after NQMI.[83] However, the beneficial effect must be tempered in that the definition of extension of infarction/reinfarction in the DRS Study was based purely on re-elevation of CPK-MB levels (i.e. biochemical and not clinical grounds). This led to an over-estimation of this

complication[13] and therefore, an over-optimistic beneficial effect of diltiazem.

b) Late use of calcium antagonists

Wong et al analysed a cohort from the Multicenter Diltiazem Post Infarction Trial (MDPIT) in which 235 NQMI patients with first MI were randomised to diltiazem, and 279 patients to placebo. Reinfarction within 6 months, occurred in 2 of the diltiazem group, versus 17 in the placebo group ($p=0.001$). Late reinfarction (after 6 months) and mortality were similar in both groups.[93] This did not confirm the original report of MDPIT which included all acute infarcts and suggested a significant reduction in 1-year cardiac events (cardiac death or non-fatal MI) in patients on diltiazem, which appeared to be especially beneficial in patients with a first NQMI.[107][35] The possible mechanisms proposed by Wong et al for the beneficial effect of diltiazem on reinfarction within 6 months, include:

i) reduction in vascular spasm
ii) reduction in heart rate and blood pressure
iii) possible antiplatelet effect which may help stabilise the lesion in the infarct-related artery.

However, again the acceptance of these positive results can only be made with strong reservations. The MDPIT Study enrolled patients from day 3-15 after the NQMI and therefore excluded many of the most unstable patients with the highest early mortality. Also excluded were those felt to have a high likelihood of undergoing cardiac surgery. The long-term

incidence of reinfarction was not affected by diltiazem and therefore is possibly due to late reinfarctions representing progression of atherosclerotic disease. This was supported by the random distribution of the location of late as compared to the early reinfarctions.[93] Furthermore, the MDPIT Study revealed that the group of patients (after NQMI or QMI) with left ventricular dysfunction who received diltiazem, had a worse long-term outcome. There was a 41% higher cumulative cardiac event rate (including mortality) compared with placebo in the 20% of patients showing pulmonary congestion on chest x-ray (CXR) done during admission with the index MI.[108]

Using the MDPIT data base again, it was shown that first NQMI and first inferior QMI have a 48% reduction in event rates, whereas first anterior QMI had a 25-30% excess event rate when treated with diltiazem. This appeared to reflect the degree of LV dysfunction since NQMI and inferior QMI had essentially normal LVEF. Possible mechanisms for the worse prognosis in LV dysfunction include the negative inotropic effect or neurohormonal activation of diltiazem. Further subset analysis of the MDPIT showed that in patients with NQMI, the overall frequency of CXR pulmonary congestion was low (13%). This group when treated with diltiazem, had paradoxically 0% cardiac mortality and a 6% cardiac event rate compared to the 20% event rate for placebo.[108] This sharp contrast, especially when compared to anterior QMI, suggests different mechanisms of pulmonary congestion: in NQMI this may be a 'stunned myocardium' i.e. reversible diastolic LV dysfunction in viable myocardium; in QMI congestion of the lungs reflects

reduced LV systolic function. Diltiazem is beneficial to the former, and harmful to the latter.[108]

Meta-analysis of therapy with various calcium antagonists after MI has revealed a disturbing excess mortality averaging 6% among patients taking active agents.[109] However, when revised to include only trials with diltiazem and verapamil, (DAVIT-II, the second Danish Verapamil Infarction Trial) i.e. the non-dihydropyridine group of calcium antagonists, meta-analysis suggested an overall risk reduction in cardiac events in NQMI which may be as high as 35% when compared to placebo.[108]

Therefore, in summary, the following are the known effects of calcium antagonists after NQMI:[110]

i) Nifedipine has no beneficial effects; may be harmful

ii) Verapamil has shown no preventative effect on death, reinfarction or post-infarct angina.

iii) Diltiazem is the only agent shown to have short and long-term benefits on clinical outcome (reinfarction <6 months), but not on survival.

The American College of Cardiology / American Heart Association Joint Task Forces' guidelines, regard diltiazem as possibly effective for use in patients after NQMI and recommend its use.[111]

The question as to whether diltiazem should be given for the 'at risk period' and then withdrawn, as it has no positive effect in the long-term, has never been addressed.

5) **ACE-Inhibitors**

There is no reason to believe that angiotensin converting enzyme inhibitors should be less effective in NQMI than in QMI patients with LV dysfunction. A study using captopril in NQMI has shown therapeutic effects not only on LV dysfunction, but also on ischaemia with a significant reduction in the duration of ambulatory ST depression 6 months after the index MI.(112)

9B. MANAGEMENT RECOMMENDATIONS: THROMBOLYSIS

Thrombolysis in QMI has been proven to be beneficial in terms of survival in numerous well-conducted trials. The simplistic arguments of restoring perfusion to an ischaemic segment of myocardium, thus limiting the infarct size, may however, not be directly transferable to the case of thrombolysis in NQMI. This is particularly so in view of the underlying pathogenetic mechanisms involved in NQMI which may not involve complete occlusion of the infarct-related artery, but may result from dynamic processes that perpetuate under-perfusion in the face of a mechanical obstruction that itself may not be critically flow-limiting.

Based on good evidence, there is not much debate about the use of thrombolytics in NQMI patients presenting with ST segment elevation. The term NQMI is usually applied retrospectively. Knowing that up to 37% of patients presenting with ST segment elevation will not go on to have QMI even without thrombolytics(69) should not alter management as awaiting the development

of Q waves defeats the objective in giving thrombolytics in the first instance.

The dire consequences of loss of myocardium and compromised LV function in acute ischaemic syndromes have encouraged the use of thrombolytics even when clinical indications are unclear. Such attempts have been made with acute MI patients presenting with ST segment depression, NQMI and even UAP (all of which overlap to a certain extent).

Numerous studies have included ST segment depression in the assessment of thrombolytic therapy. Even though coronary arterial thrombi play an important role in the acute event, subgroup analysis of patients with MI, who present with ST depression and usually evolved NQMI, in trials such as the GISSI-1[113] and the ISIS 2[114] has shown no survival benefit with streptokinase (SK) therapy compared with placebo. In fact, the vast majority of studies, using all types of thrombolytic/fibrinolytic agent, have shown no statistically significant reduction in mortality during days 0-35, even though such patients were at high risk of deaths.[115]

Furthermore, the general findings applicable to all infarcts may be even more significant in NQMI. Thrombolytic therapy for acute MI does not reduce the incidence of recurrent ischaemia or infarction as is evident from the 18-26% incidence of recurrent ischaemia reported in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) and TIMI trials. In the GISSI study, the incidence of reinfarction in NQMI patients was documented as 4% in

the streptokinase group which was actually significantly greater than in the placebo group (2%).[91]

Thus the results of the TIMI IIIB (Thrombolysis in Myocardial Ischaemia) specifically designed to look at this dilemma, and not by subgroup analysis, is significant.[68] The trial's primary objectives were twofold:

1) to determine the effects of thrombolytic therapy in UAP and NQMI; and
2) to determine the role of routine early coronary angioplasty followed by revasculation versus conservative treatment.

One-thousand four-hundred and seventy-three patients were randomised, with the primary endpoint for the tissue plasminogen activator (TPA) - placebo comparison being death, MI or failure of initial therapy at 6 weeks. The endpoint was reached in:

> 54.2% of the TPA patients versus 55.5% of the placebo-treated patients (p=NS)

Furthermore, reinfarction in NQMI patients occurred more frequently in the TPA-treated patients:

> 7.4% of "TPA" patients versus 4.9% in "placebo" patients (p=0.04)

Intracranial haemorrhage occurred in 4 of the TPA-treated group (p=0.06).

Thus, the conclusion of this study was that the addition of a thrombolytic agent is not beneficial and may be harmful.

Reasons for the lack of benefit of thrombolytic therapy in this TIMI IIIB trial, possibly include:

i) The low dose of TPA used (63mg on average). This was to reduce complications in a group with known low mortality rate.[68]

ii) The simultaneous clot dissolving and procoagulant actions of thrombolytic agents. Thrombolysis may expose the fibrin-bound thrombin which is a potent stimulus for rethrombosis.

iii) Platelet thrombi (which are more resistant to lysis than erythrocyte composed thrombi) are the type that predominate in the unstable acute coronary syndromes. In addition, thrombolytics may activate platelets directly.

There are numerous reservations about the general recommendation of this TIMI IIIB trial that thrombolytic therapy not be used routinely in patients with UAP or NQMI:

i) As mentioned before, concerning UAP and NQMI being "lumped" together, often under the title "acute coronary syndrome", these two conditions although having similar aetiology, have a different clinical course and prognosis. Thus, a general recommendation may not be applicable (if these two conditions could be differentiated prospectively).

ii) This trial studied only a subset of the total heterogeneous non-Q wave group of myocardial infarcts, enrolling only patients with ST segment depression and T wave changes, but

excluding ST segment elevation longer than 30 minutes. This group forms up to 40% of all NQMI. Also excluded were patients in pulmonary oedema, systolic BP > 180mmHg and diastolic BP > 100mmHg. Thus, recommendations regarding NQMI presenting with ST segment elevation remain unaltered.

iii) Not all the patients were comparable. Up to 12% were receiving heparin at the time of the qualifying episode i.e. they did not present with NQMI and may therefore have been in a different risk category.

iv) The use of TPA as opposed to SK may not be equivalent. Studies have shown differences where thrombolytics are used conventionally.

v) All the patients were given a calcium antagonist (diltiazem 30mg 6 hourly) which may have confounded the issue or blurred differences in outcome of UAP versus NQMI.

Even so, the current recommendations with regard to thrombolytics in NQMI can only be to restrict their use to those patients presenting with acute ischaemia and ECG evidence of ST segment elevation.

9C. MANAGEMENT RECOMMENDATIONS: ACTIVE

1. Stress Testing
2. Invasive Investigation
3. Active Intervention - Revascularisation

Recognising the differences between QMI and NQMI, aggressive approaches in management with active intervention have been recommended in the latter. The basic argument is that with an incomplete myocardial infarction, more salvage is possible. The

suggested more aggressive diagnostic approach may include a careful non-invasive search for ischaemia and/or coronary angiography, even in the asymptomatic, but selected patient. However, there is no firm evidence that this active management strategy influences the course of NQMI favourably.

1) **Stress Testing**

The rationale behind exercise stress testing (EST) is to identify residual ischaemia and thereby identify and better direct invasive investigation in such a heterogeneous group as NQMI patients.

The question raised is whether EST is a good discriminator for predicting NQMI patients at risk and its comparison to the use in QMI patients. Most studies have shown that the absence or presence of pathological Q waves had no significant effect on the ability of the EST to identify risk subset of survivors of acute MI.[45][116]

Within the NQMI group of patients, the timing of the EST may also be significant. Since much of the recurrence of ischaemia in NQMI patients occurs in the immediate post-index MI period, early EST done pre-discharge, is preferable to EST done 4-6 weeks later at the first outpatients visit. In a Swedish study evaluating the use of pre-discharge EST in patients with NQMI, it was confirmed that ST segment depression, occurrence of angina and low peak load at exercise were independent predictors of future severe angina that necessitated rehospitalisation and investigation.[117] Not only positive results are useful; Sia et al showed that

negative results in the early EST after NQMI predicted absence of triple vessel coronary artery disease or critical stenosis of one vessel with an accuracy of 92%.[118]

However, the use of EST as ultimate risk stratifier with NQMI must be cautious. The Multicenter Post-Infarction Research Group showed that early low level EST is of limited value. In studying patients with first NQMI who were able to exercise, ST depression during exercise identified patients with a 71% incidence of cardiac events within 1 year versus 5.3% for those without ST segment depression ($p=0.002$). Yet, even with this statistically significant result (odds ratio of 45), on subgroup analysis of patients without presence of pulmonary congestion, the exercise test had no discriminatory value. They concluded that low level exercise testing has a limited role after uncomplicated NQMI, but is useful in patients with clinical markers of higher risk.[119]

When considering performing this test in all NQMI patients pre-discharge, knowing the frequency of positive results may be useful, especially if it is to be followed by active intervention. Gibson, in studying the clinical and functional differences between Q and NQMI reported that 55% of the NQMI patients had either angina or ST segment depression during pre-discharge EST (versus 40% of QMI patients [$p<0.03$]).[55]

2) **Invasive Investigation**

Coronary artery bypass grafting (CABG) has been shown to improve prognosis (survival) in patients with left mainstem stenosis or triple vessel disease (TVD) and impaired left

ventricular function.[120][121][122] Patients with single vessel disease may also benefit from revascularisation, CABG or percutaneous transluminal coronary angioplasty (PTCA), not so much for prognosis/mortality, but for symptoms or further recurrence of ischaemia.

Armed with this powerful argument and without research/trial-based limitations, pursuit of the knowledge of coronary anatomy becomes an overwhelming or irresistible goal once triggered off by the patients experience, however transient, of chest pain.

The data concerning the value and applicability of cardiac catheterisation, which is always done with a view to revascularisation, needs to be re-evaluated for NQMI.

Hence the importance of the two studies: TIMI II, with specific regard to sub-analysis for NQMI, and the second part of TIMI IIIB both of which addressed the role of routine early coronary angiography followed by revascularisation when anatomy was suitable, versus early conservative strategy (coronary angiography followed by revascularisation if initial medical treatment failed).

In the 6 weeks of follow-up in TIMI IIIB, which enrolled patients with ST segment depression (and included UAP and NQMI) and randomised them on admission to either invasive or conservative strategies, the results were:[68]

	Catheteri-sation	Revascu-larisation	Deaths MI or Positive EST	Endpoint in patients ≥ 65 years
Early Invasive Group	98%	61%	16.2%	7.9%
	(p<0.01)	(p<0.001)	(p=NS)	(p=0.02)
Early Conserva-tive Group	64%	49%	18.1%	14.8%

Thus, in general, equivalent results (occurrence of the primary endpoint of death, MI or positive EST by 6 weeks) could be achieved by using either early conservative or early invasive strategy. (In the NQMI subset, excluding the UAP patients, only a trend could be demonstrated towards an improved 6-week outcome in the invasive group.)

Additional observations were made:

1. In patients ≥ 65 years, the primary endpoint was reached in 7.9% of the invasive group; significantly lower than 14.8% in the conservative group.
2. There was also a lower incidence of re-hospitalisation, days of hospitalisation and use of anti-anginal drugs in the early invasive group.

The TIMI II Study inclusion criteria were ST segment elevation with chest pain (>30 minutes, but <4 hours)). In a subanalysis to determine whether invasive or conservative strategy was favourable, only first infarct patients, all of whom had been given TPA, were included and the day 2 ECG interpretation was used to differentiate QMI from NQMI.[22]

The findings were similar to TIMI IIIB in that, at 6 weeks, the occurrences of reinfarction, death or combination were equivalent in patients assigned to the invasive or conservative post-lytic management strategy - this regardless of the presence or absence of Q waves.

Therefore, in essence, early invasive/active investigative management is as good as early conservatism. A number of points, however, have to be borne in mind:

- The conservative strategy in these TIMI studies was not really conservative, but expectant and actively sought for recurrence of ischaemia in the patients (e.g. by EST). The mean time for cardiac catheterisation after the index MI in the conservative strategy group in TIMI IIIB was 7.1 days and since 64% of this group's patients underwent catheterisation, it is not entirely surprising the results as compared to active management are similar.

- These TIMI studies each included only specific subsets of all NQMI infarctions (which is probably the correct way of analysing recommendations for such a diverse group at NQMI). The results cannot be generalised and be applied to all NQMI.

- Exceptions to the overall recommendations need to be noted. Age was shown in TIMI IIIB to be an important consideration. This is in keeping with the findings of Nicod et al studying NQ and QMI in a large patient population that showed higher mortality in NQMI patients

only in those >70 years.[28] This strengthens the argument that a general policy of invasive management may not be appropriate in the younger patient population (≤70 years) without ischaemic events.

- The conservative strategy in TIMI IIIB began on admission and thus encompassed the entire initial period of instability which is usually during the admission period. *Therefore, the dilemma of what type of management (conservative or investigative) is indicated in the group of patients who remained stable or achieved discharge without complication is yet to be addressed.*

- The follow-up durations in these studies are short (6 weeks). Longer term follow-up is required to confirm these early observations.

- Any recommendation in favour of catheterisation of asymptomatic post-infarct patients still assumes that prophylactic revascularisation with CABG or PTCA will prolong life and/or prevent reinfarction. Prognostic benefit has only been shown, as mentioned before, with left mainstem or TVD and impaired LV function.[120][121]

3) Active Intervention - Revascularisation

a) PTCA

Percutaneous transluminal coronary angioplasty has been shown to be successful in NQMI. A study specifically looking at this issue, by Robert et al, showed that PTCA was successful in 87% of 68 patients with angina, an average of 2.3 months

after NQMI.[92] However, this study was uncontrolled and most of these patients had single vessel disease with preserved LV function, in whom a favourable outcome was expected. It can thus not be an endorsement of PTCA in all patients after NQMI, particularly in those with complex multivessel disease. Furthermore, recurrence of angina in patients who underwent PTCA for angina after NQMI varies from 20% to 41%.[24][92] This suggests a relatively high clinical restenosis rate. PTCA performed in NQMI patients with recurrence of ischaemia appears justifiable and yet, in the TIMI IIIB Study, PTCA was performed in the early invasive group even if the patients settled down. PTCA was also done to major arteries other than the culprit artery - in order "to maximise the relief of ischaemia".

What about the timing of PTCA? In the group of patients that receive thrombolytics, there appear to be some answers. Routine PTCA in the first 48 hours following thrombolysis, offers no benefit and is not recommended.[117] Immediate angioplasty following thrombolysis, as compared to delayed PTCA or conservative management, has not been shown to improve LV function and is associated with a trend to increased in-hospital and one-year mortality.[123] Delayed/deferred PTCA (i.e. within 48 hours after thrombolysis), compared to a more conservative approach, has been associated with increased incidence of emergency CABG and no significant reduction in rates of reinfarction or mortality.[124] On the other hand, angioplasty guided clinically (by recurrence of ischaemia) or conservative treatment is not associated with any lower survival, but is associated with increased incidence of

symptomatic post-discharge angina hospital re-admissions and possibly costs.[125]

The issue of primary angioplasty also needs to be considered. Apart from being another cause of NQMI, by aborting the development of QMI, preliminary results suggest that patients who have had primary PTCA have a better prognosis than those treated with thrombolysis, possibly having half the reinfarction or mortality at 6 months.[126]

b) CABG

It was shown, some time ago, that coronary artery bypass grafting (CABG) done within 30 days after an acute MI is safe.[127] Studies assessing the usefulness of CABG in NQMI have been few and limited to the assessment of relief of symptoms. A prospective study of patients treated with CABG within 3 months of NQMI shows on long-term follow-up (16 months) that there was a 78% incidence of angina-free survival.[128][127]

In summarising 'Management Recommendations', with regard to active investigation and intervention, evidence is still lacking in support of its general recommendation in NQMI. Many studies or findings suggest aggressive management, but few actually show that this translates into improved survival. Routine angiography on all NQMI patients before discharge does influence the course of NQMI favourably, but this only for symptoms (post-discharge angina and re-hospitalisation) and not survival.[124] In order to catch all

cases where intervention may have benefit, the net has to be cast widely. The joint task force of the American College of Cardiology and the American Heart Association formulated guidelines for coronary angiography and placed NQMI without any qualifications or restrictions into Class I - i.e. definite indication for angiography.[108] The problem with such wide netting is that the catch may be unexpected and unwanted. Therefore, if stenosis seen on angiography is equivocal, EST (or radionuclide stress testing) is then requested and if positive, one may feel compelled to do revascularisation even if the patient is stable and his lifestyle unrestricted.

The question remains: how should NQMI be managed? Broadly speaking, either as UAP with an aggressive strategy with a view to revascularisation, or as an evolved MI with conservative treatment supported by investigation if indicated. These are grounds for the performance of a study in NQMI, in which the high incidence of recurrence may be an advantage in that it is easier to determine the ideal strategy.

PROJECT OBJECTIVES

PROJECT OBJECTIVES

1. PROJECT PURPOSE

The purpose of this study is to determine and analyse the experience of the Coronary Care Unit of Groote Schuur Hospital (GSH) with NQMI with specific regard to diagnosis, management, investigation and outcome.

2. PROJECT AIMS

The aims of this analysis are:

1) to compare the outcome of patients with NQMI at GSH to that in other studies.

2) to assess the recurrence of myocardial ischaemia in this group of patients.

3) to determine and compare the outcomes of patients managed more conservatively as opposed to those who underwent investigation and active intervention.

In achieving these aims, additional conclusions or analyses will be possible:

1) a statistical audit of cardiac catheterisation in NQMI (indications, complications, findings, recommendations and outcome).

2) the determination of accuracy of localisation of site of myocardial infarction in the absence of localising pathological Q waves

3. IMPLEMENTATION OBJECTIVES

Investigation of patients with ischaemic heart disease is associated with morbidity, mortality and considerable cost. Thus knowledge of the extent of investigation needed in managing patients with NQMI may be of great advantage and benefit in justifying risks and especially where resources (staff, experience and equipment) are limited.

RESEARCH METHODS

RESEARCH METHODS

1. DEFINITION: NON-Q WAVE MYOCARDIAL INFARCTION

As there is an interest in characterizing the make-up and location of NQMI and determining any factors to further risk stratify NQMI, a broad definition of NQMI is required to encompass all these patients.

NQMI have previously been equated to:-

* nontransmural infarcts
* ST segment or T wave infarcts
* subendocardial infarcts.

However, these terms are inaccurate and exclusive.

Thus the criteria for admission into this study henceforth also referred to as the Groote Schuur Hospital (GSH) Study, as acute NQMI were a triad:

1) History
2) ECG changes
3) CPK enzyme rise.

1) History: Suggestive of myocardial ischaemia i.e. typical ischaemic chest pain. Obviously this excluded those patients with no previous history of ischaemic heart disease and who now presented with silent myocardial infarction. It was, however, unlikely that such a patient would be admitted to the Coronary Care Unit.

2) ECG changes - excluding new pathological Q waves (or development of them during the hospital admission without evidence of recurrent infarction). For the purpose of this study the definition of Non-Q MI was used in its broadest meaning i.e. absence of new pathological Q waves. Thus, any changes in the standardized 12-lead electrocardiographic tracing were acceptable except for pathological Q waves present in >2 leads which would be defining criteria for a NQMI by the Minnesota code and WHO categorization.[74] Pathological Q waves were defined as: Q waves broader than 0,04 sec and deeper than 25% of the subsequent R waves. Previous Q wave myocardial infarction was not excluded provided it was clear that the present index infarct was clearly a NQMI, involving a different area and not a "reinfarction" in a previous QMI area. Thus it was evident that this definition of NQMI would also include:

a) pathological R-wave infarcts:
   - true posterior (Q wave) myocardial infarction (R wave >S wave and >30mS in V_1 or V_2) which are not considered to be true NQMI by some investigators.
   - >50% loss of R-wave voltage compared to baseline.

b) acute myocardial infarction presenting with new LBBB or developing LBBB before evolving Q-waves.

c) subendocardial or "ST segment" infarcts.

d) AMI that are not localisable e.g. LBBB, but these would be excluded from analysis of outcome and prognosis as is generally accepted in other studies.

e) Previous Q wave MI.

f) Aborted Q wave MI - by thrombolysis. Subanalysis of the results would take these factors into consideration.

3. CPK Rise: A diagnostic CPK enzyme rise of acute MI is generally considered to be twice the upper normal limit for CPK at a particular laboratory excluding other non-cardiac sources. (However, some studies have included CPK only 150% of their top laboratory normal value.[75][92] Although MB iso-enzymes are more specific (they may be less sensitive) and testing for them is available at GSH, this result was available in only a minority of patients. However, it is not a requirement for diagnosis, especially if the triad of diagnostic features is present, and is used more particularly in doubtful cases. The abnormal elevation of CPK had to occur before any intervention was performed.

The triad had to be fulfilled. Hence UAP was excluded.

2. STUDY DESIGN

1) **Patient recruitment**

Patients for this study were recruited by retrospective folder or admission note analysis of the primary index admission. This is facilitated by the keeping of a separate copy, by the Cardiac Clinic, of the clerking and admission notes of every patient admitted to the GSH Coronary Care Unit.

2) **Follow-up**

Follow-up and outcome were determined again from folder analysis and by telephonic and postal communication.

3. PATIENT POPULATION

3A. STUDY POPULATION

The study population consisted of all patients admitted to the Coronary Care Unit (CCU), Groote Schuur Hospital (GSH) between 1st January 1990 and 31st December 1993, a period of 4 years. From this group were selected all those who fulfilled the triad of criteria for the diagnosis of acute NQMI: 181 patients.

Routine Management:

Routine management in the CCU consisted of aspirin, IV heparin and the introduction of beta-blockers. Calcium antagonists were not given. Thrombolytic agents were administered if accepted indications existed:-

1) typical acute chest pain lasting > 30 minutes, unrelieved by nitrates.
2) ST segment elevation >1mm in 2 contiguous leads.
3) Total duration of symptoms lasting <6 hours.

Cardiac catheterisation during the primary admission was not routine practice. The aim of cardiac catheterisation was to define coronary artery anatomy. The policy of the Cardiac Clinic was to act (i.e. perform revascularisation, either PTCA or CABG) on lesions only if accompanied by the occurrence of symptoms (and not prophylactically). During the study period, the cardiac catheterization laboratory was not very aggressive with PTCA. Stenting or other percutaneous revascularisation methods were not available during the time period of this study.

Exercise stress testing or other tests of evoking ischaemia were not routine practice at GSH, either pre-discharge or at the first follow-up visit.

Follow-up occurred at the Cardiac Clinic, Medical Outpatients or Day Hospitals and by Family Practitioners. The policy at GSH was to discharge well and stable patients from follow-up clinics to the community.

Factors or characteristics analysed:

Each of the 181 NQMI patients was analysed with respect to:-

1) Demographic features (age, gender, race);
2) Risk factors or previous medical history of angina, myocardial infarction or ischaemic heart disease, hypertension, diabetes mellitus, hyperlipidaemia, cardiac failure, peripheral vascular disease; history of smoking or heavy alcohol intake; use of aspirin prior to the index NQM;
3) Time periods: duration of preceeding angina, duration of acute pain, time from pain onset to admission in GSH;
4) Admission characteristics: blood pressure, evidence of cardiovascular instability, ongoing chest pain, arrhythmias;
5) Laboratory investigations: CPK enzyme peak, CPK-MB iso-enzyme positivity, cholesterol level. (CPK enzyme levels were taken routinely on admission, at 12 and 24 hours)(MB iso-enzyme was considered positive if the CPK-MB isoenzyme level was >6% of total CPK level);
6) ECG findings;
7) Initial management: thrombolysis, heparin use, inotrope use;
8) Cardiac catheterisation and angiographic findings and definitive in-hospital management: medical or revascularisation;
9) In order to determine what proportion patients with myocardial infarction and particularly NQMI formed of the annual work-load of the coronary care unit, all patients admitted to the

GSH CCU in 1993 were analysed as to the reason for admission. If this was a myocardial infarction, the following factors were determined:

- QMI or NQMI
- use of thrombolytics
- ECG location.

3B. ELECTROCARDIOGRAPHIC ANALYSIS

This was based on admission and subsequent daily ECGs which were also requested whenever there was a change in the condition of the patient. All these were analysed with respect to development of Q waves, which if found, resulted in the exclusion of the patient from this study. i.e. the non-Q wave diagnostic feature was not based on the admission ECG.

In many instances it is difficult to assess accurately the specific infarct subtype (Q vs NQMI) on admission. Some patients develop Q waves rapidly and others will evolve Q waves over the course of days.[66] A natural history study of early NQMI has shown that 20% of patients who on admission "had" a NQMI with ST segment elevation developed Q waves subsequently and 15% with ST segment depression and/or T inversion developed Q waves subsequently.[69]

All these ECGs were assessed to determine NQMI location. NQMI localisation appears to have prognostic implications. Location was determined by the leads in which primary ECG changes occurred, as based on criteria for infarct location described by Schamroth[129] and Rowlands.[130] The primary ECG changes in decreasing order of importance or validity are:

1) ST segment elevation (in 2 contiguous leads), primarily and
2) T wave inversion (in 2 contiguous leads)
3) ST segment depression in combination with T wave inversion.
4) R wave changes:
   - peaking/dominance in V_1 and V_2
   - loss of R wave height (regression) in anterior chest leads.

ST segment depression alone was not used as it is considered to be a poor localiser.[30][131]

Localisation was by territory with the following criteria:

Inferior:	(above ECG changes in 2 leads of II, III and aVF)
Inferoposterior:	(as for inferior with peaking or dominant R wave in V_1 or V_2)
Inferolateral:	(as for inferior with changes in V_6, I or aVL)
Posterior:	(dominant R wave in V_1 or V_2)
Anterior:	(equivalent to extensive anterior: changes in V_1 to V_5 or V_6)
Anteroseptal:	(changes in V_1 or V_2 to V_3 or V_4)
Anterolateral:	(changes in V_4 to V_6 plus I or aVL)
Lateral:	(changes in I and aVL)

Another category termed: "widespread ST segment depression" and often labelled as subendocardial location, was identified if there was:

* widespread ST segment depression
* without inverted T wave localization or NQMI location in multiple areas

* and these changes were persistent.

Non-localisation: i.e. not localizable to one territory

(* ST segment depression only i.e. no T inversion or

* T inversion in 2 territories)

The admission ECG specifically and prior to any acute management e.g. thrombolysis, was assessed for:

* ST segment elevation
* ST segment depression
* T inversion (in the absence of ST segment elevation)
* ST segment depression (in the absence T inversion)

as these features have been shown to influence the subsequent course in NQMI patients.

Further analysis of the positive predictive and other statistical value of ECG in localisation of NQMI was performed in the group of patients who underwent LV angiography in whom specific regional wall motion abnormality was considered to be the gold standard for defining NQMI location. Angiograms of patients who had had previous myocardial infarction were excluded from these epidemiological tests.

3C. CARDIAC CATHETERISATION

Cardiac catheterisation was performed in 93 patients during the primary admission with the index NQMI - this was termed "early cardiac catheterisation" (the majority within 96 hours of presentation). None of these catheterisations was for a rescue angioplasty or a primary angioplasty.

Coronary angiography and left ventriculography were performed using multiple views of the right and left coronary systems in right and left anterior oblique projections to define the coronary anatomy.

In order to examine whether NQMI patients should be managed with active intervention or not, it was important to extract a group of patients that was investigated just for the fact that they had NQMI. The indications and reasons or justifications/intentions of the attending cardiologist, as stated in the written records, for this early cardiac catheterisation were analysed.

Indications for Cardiac Catheterisation:

1) NQMI: Cardiac catheterisation done purely for the presence of a non-Q myocardial infarct.
2) ECG: "ischaemic looking" ECG changes e.g. deep symmetrical T inversion in the anterior chest leads suggesting possible proximal LAD stenosis; widespread significant ST segment depression.
3) NQMI plus "ischaemic-looking ECG": presence of NQMI plus ECG which appeared to show persistent ischaemia.
4) Positive EST: A low level (70% of maximum) exercise stress test was performed during the primary admission in only 9 patients to determine inducible ischaemia in "incomplete myocardial infarction".
5) Unstable angina pectoris history: History of severe angina pectoris preceding the index NQMI. The NQMI was considered to be a non-final event or a small infarct not resolving the underlying problem.
6) Unstable immediate outcome or ongoing chest pain.

7) UAP - post infarct angina.

8) Dissection of aorta presenting with NQMI.

Contraindications to cardiac catheterisation were determined:

1) cardiac catheterisation was indicated for reasons of cardiac ischaemia or NQMI, but considered inadvisable because of co-morbidity e.g. poor lung function, morbid obesity, bedridden, poor left ventricular function or cardiomyopathy, cerebrovascular disease.
2) patient refusal.

Complications as a result of catheterisation were noted.

The **findings** at cardiac catheterisation were assessed:

1) haemodynamic: LV end diastolic pressure
2) angiographic: a) left ventricular and b) coronary

All the angiograms (121) performed in this group of NQMI patients were analysed. To ensure uniformity of inter-pretation, they were all reviewed by one investigator and over a short period of time (4 days) to maintain consistency. This was done blinded to the ECG findings or previous history of myocardial infarction. Where marked discrepancies were noted with the initial angiogram report, re-analysis was performed. If the findings were subsequently found to be in keeping with

the history or ECG evidence of previous myocardial infarction, or if another myocardial infarction was sustained after the index NQMI and before cardiac catheterisation was performed, these angiograms were considered as being invalid for further analysis.

a) LV Angiography:

This was assessed for:

- impaired LV function
- dilatation of LV
- regional wall motion abnormality:

i) type (hypokinesia, akinesia, dyskinesia and aneurysmal);

ii) site

The findings were then used to determine NQMI location by angiography.

b) Coronary angiography:

Assessment was made of:

- presence of occlusive coronary artery disease (whether or not the considered culprit lesion was occluded or patent);
- vessel involvement (single, double, triple, and/or mainstem, vasospasm);
- culprit vessels (primary and if difficulty to ascertain, a secondary culprit vessel was noted)

(The identification of the culprit vessel or Infarct-Related Artery (IRA) is based on the severity of stenosis in relation to the site of regional wall motion abnormality. Thus, the IRA may be defined as the vessel

that was most likely responsible for the abnormalities observed on LV angiography.);

- culprit vessel (IRA): occlusion or patency;
- collaterals: these were graded according to Rentrop's classification[89].

Grade 0 = no visible filling of collateral vessels

Grade 1 = collateral filling of branches of the occluded or stenosed vessel without any dye reaching the epicardial segment of that vessel (i.e. very poor collaterals)

Grade 2 = partial collateral filling of the epicardial segment of the diseased vessel

Grade 3 = complete filling by collateral vessels of the culprit vessel.

Early catheterisation refers to catheterisation during the primary hospital admission (not necessarily during the CCU stay) as a result of an indication determined during the CCU admission.

Late catheterisation refers to those investigations indicated only after discharge from CCU following admission with the primary NQMI. This was considered as failure of initial conservative management.

3D. FINAL LOCALISATION OF NQMI:

In order to determine the final location of the NQMI, results of all investigations performed in an individual were considered. They were ranked in decreasing order of certainty or validity with regard to power of localisation:

- LV angiography: regional wall motion abnormality
- echocardiography
- nuclear LV imaging
- coronary angiography (supposed culprit vessel)
- ECG:
  - ST segment elevation
  - pathological R wave
  - T inversion
  - ST segment depression and T inversion

3E. MANAGEMENT

The records, particularly of those who underwent early catheterisation, were analysed to determine what recommendations were given or what action followed, viz.:

1) medical treatment;
2) percutaneous transluminal coronary angioplasty;
3) coronary bypass grafting;

and for alternative action if the patients subsequent course indicated it (e.g. recurrence of symptoms).

Early revascularisation was considered to be the total of PTCA and CABG as a result of early catheterisation.

Late revascularisation included all the PTCA and CABG patients in whom these procedures were recommended as a result of late catheterisation which was performed for failure of initial conservative management or where medical (only) treatment had been recommended at the earlier procedure.

4. PROGNOSIS, ANALYSIS AND FOLLOW-UP

4A. IMMEDIATE OUTCOME

The immediate course (and status during the first 24-48 hours) of admission to the CCU was assessed and the patients were classified as stable or unstable.

The unstable group included:

1) Cardiovascular instability:
   - haemodynamic instability (cardiogenic shock)
   - requiring inotropes
   - significant pulmonary oedema
2) Ongoing ischaemic chest pain
3) Arrhythmia
   (life-threatening e.g.
   - ventricular fibrillation
   - symptomatic ventricular tachycardia
   - symptomatic bradycardia e.g. CHB)

This group could be considered to have required intensive care management and intervention for subsequent survival.

4B. FOLLOW-UP

Follow-up of the patients was essential in order to determine the validity of factors in risk stratification of NQMI and its management: conservative versus active intervention. A minimum follow-up period of one year was striven for. This was achieved in 166 patients (92%) including accumulated deaths over a period of one year. Longer periods of follow-up were impractical as there is a high incidence of loss of follow-up by Groote Schuur Hospital

with attendance at other regional hospitals and general practitioners. (Stable patients are routinely discharged from further follow-up at GSH.) Those patients about whom less than one year of information subsequent to the index NQMI was available by folder analysis, were contacted by telephone or post.

Factors noted in follow-up were: (endpoints in the study)

1) Recurrence of ischaemia:
   - patients with AMI at GSH do not, as is sometimes recommended, routinely undergo tests to provoke ischaemia e.g. EST, thallium or sestamibi stress tests, holter monitoring; rather, recurrence of ischaemia is awaited by the spontaneous declaration of further symptoms.
   - recurrence was defined as being early, following recognised definitions, if it occurred within 3 months of the index NQMI.
   - although recurrence was considered to be a failure of either conservative or active management and thus an endpoint in this study, the patients were still followed up to the minimum period of a year to determine re-admission or mortality.
2) Re-admission for recurrence of ischaemia; taking into account:
   - the need for, results and recommendations of late cardiac catheterisation
   - late revascularisation.
3) Reinfarction
4) Cardiac failure subsequent to discharge after index event.
5) Mortality:

a) time interval after index events

   i) in-hospital (early): a generally reported term

   ii) subsequent to discharge

b) cause:

   i) cardiac - this included all deaths attributed to the heart or myocardial infarction, i.e. intra- or peri-operative (less than 30 days after cardiac surgery [CABG])

   - as a result of reinfarction, ischaemia or cardiac failure.

   ii) non-cardiac

5. STATISTICAL METHODS

Patient data was captured on a personal computer using Paradox 4.0 (Borland), a relational database management programme. Data was analysed using Statgraphics 6.1 (Manugistics) and Epiinfo 5.00 (Centers for Disease Control, Atlanta / World Health Organisation, Geneva). Continuous data are presented as mean $\pm$ standard deviation. Frequencies and outcomes were examined and compared in a fourfold tabular analysis. Categorical variables were analysed by Chi-square and Fischer exact test for small numbers. Continuous variables were compared using the Student's T-test.

Survival curves were determined by Kaplan-Meier survival probability methods. The log-rank (Mantel-Haenszel) statistic was used for comparing survival rates and time to event variables. When analysing risk factors,[132] variables found to be significant by univariate analysis were then entered into the model of stepwise

logistic regression to identify independent predictors or subsets of variables that in combination were good predictors.
Further multivariate analysis was performed by means of the discriminant function analysis model (with stepwise analysis to maximise the chi-square value) to evaluate the independent importance of prognostic variables. This was done for following endpoints:

1) outcome (immediate)
2) mortality (specifically cardiac at 12 months)
3) recurrence

P values of <0.05 were considered statistically significant. (However, in the examination of multiple subgroups where it is difficult to interpret a claim of statistical significance at a given p value,[104] the Bonferoni argument[133] was considered, and the p value for significance was reduced.)

6. ETHICAL CONSIDERATIONS

Since this research project is retrospective, ethical considerations beyond confidentiality of patient information do not apply.

FINDINGS AND RESULTS

FINDINGS AND RESULTS

1. CCU ADMISSION STATISTICS

A. 1990 - 1993

Analysis of population in NQMI study:

Total number of NQMI patients in 4 years, 1990-1993 (fulfilling admission criteria for study) admitted to GSH CCU = 181

1990 - 32 NQMI patients

1991 - 43 NQMI patients

1992 - 52 NQMI patients

1993 - 54 NQMI patients

NQ versus all infarcts (1991) = 43/320 = 13.4%

(1993) = 54/316 = 17.1%

NQ versus total admissions 1990-1993 = 6.2%

Duration of admission to CCU:

= 3.66 days (range 1-11 days)

1993 CCU TOTAL ADMISSIONS

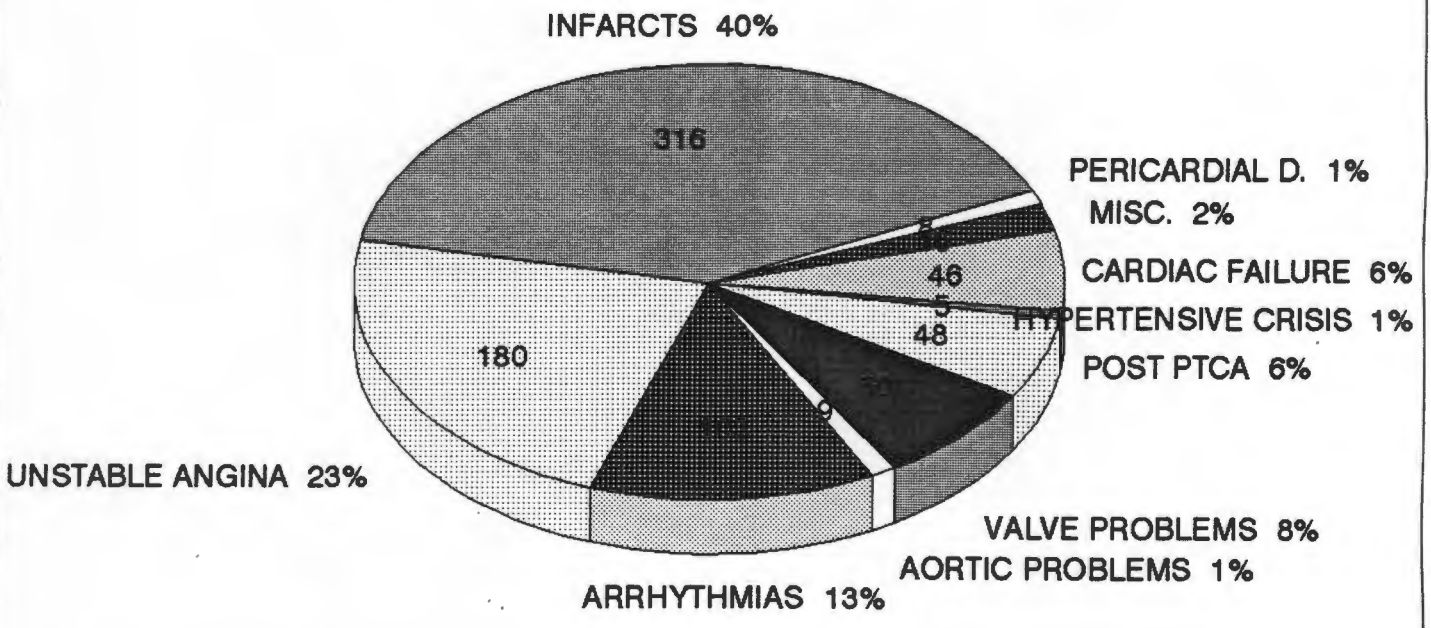


Figure No.5: The frequency of admissions by diagnosis to CCU in 1993.

B. TOTAL CCU ADMISSIONS IN 1993 = 791
PATIENTS

DIAGNOSIS/REASON FOR ADMISSION	NUMBER	PERCENTAGE
UNSTABLE ANGINA PECTORIS	180	22.8%
MYOCARDIAL INFARCTS	316	39.9%
ARRHYTHMIA (incl. for Cardioversion)	103	13.0%
CARDIAC FAILURE	46	5.8%
VALVE PROBLEMS (both Native and Prosthetic)	60	7.6%
PERICARDIAL DISEASE	8	1.0%
AORTIC DISEASE (incl. dissection, aneurysm)	9	1.1%
HYPERTENSIVE CRISIS	5	0.6%
ADMISSION POST PTCA	48	6.1%
MISCELLANEOUS	16	2.0%

LOCATION OF INFARCT: QMI vs NQMI

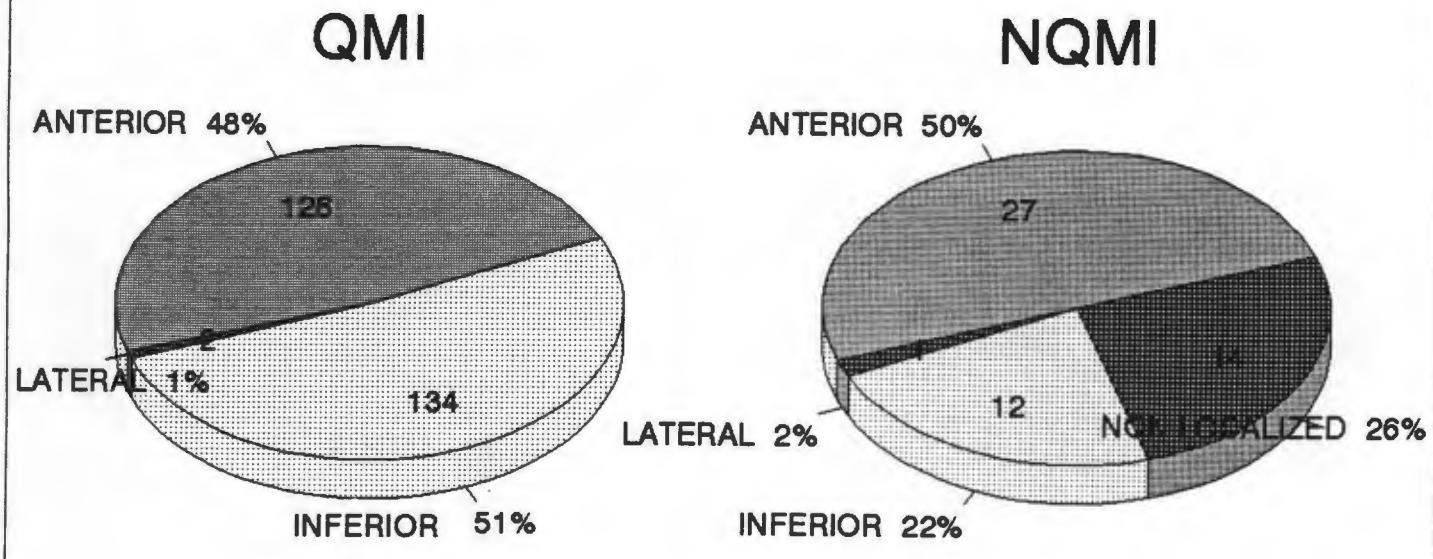


Figure No.6: Location of Q wave and non-Q wave infarcts in patients admitted in 1993.

MYOCARDIAL INFARCTS 1993

TOTAL **= 316 PATIENTS (39.9% OF ALL ADMISSIONS)**

TYPE

Q WAVE INFARCTS	= 262	(82.9% OF ALL INFARCTS)
NON-Q WAVE INFARCTS	= 54	(17.1% OF ALL INFARCTS)

LOCATION

LOCATION (BY ECG)	ALL MI	QMI	NQMI
ANTERIOR	153 (48.4%)	126 (48%)	27 (50%)
LATERAL	3 (0.9%)	2 (0.8%)	1 (1.9%)
INFERIOR	144 (45.6%)	134 (51%)	12 (22%)
NON-LOCALISED	14 (4.4%)	0	14 (26%)

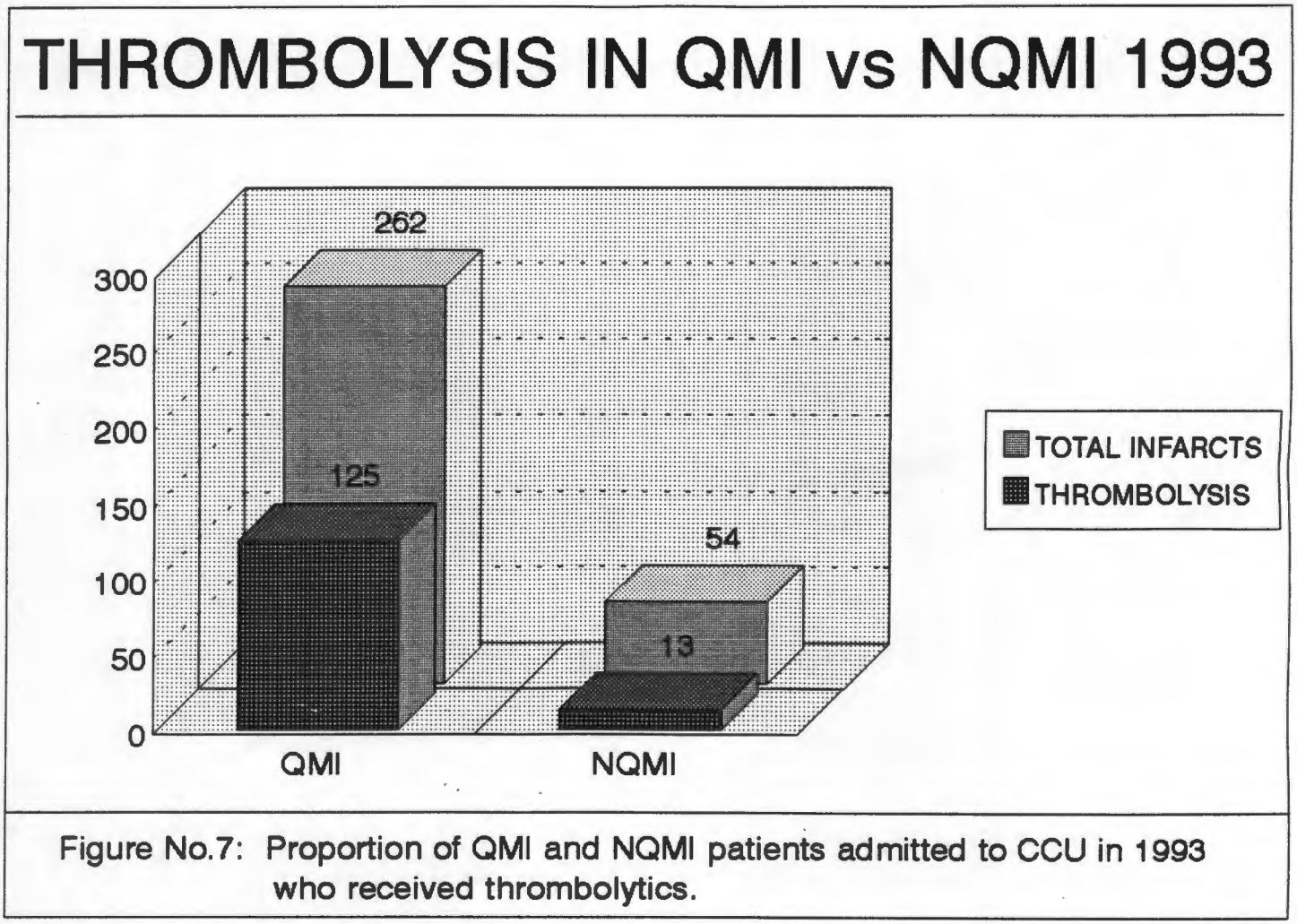


Figure No.7: Proportion of QMI and NQMI patients admitted to CCU in 1993 who received thrombolytics.

THROMBOLYSIS IN 1993

THROMBOLYTIC USED	= 138	(43.7% OF ALL INFARCTS)
QMI THROMBOLYSIS	= 125	(48% OF ALL QMI)
		(p=0.001)
NQMI THROMBOLYSIS	= 13	(24% OF ALL NQMI)

2. DEMOGRAPHICS OF NQMI 1990-1993

AGE:

mean 55.3 ± 10.7 years
range 28 to 79 years

GENDER:

	Total No.	%	Average Age
Females	64	35.3	57.3 ± 9.7 years
			(p=NS)
Males	117	64.6	54.2 ± 11.1 years

RACE / GENDER GROUPS: (as recorded by the hospital computer)

White	male	21
	female	6
Coloured:	male	94
	female	53
Indian:	male	0
	female	3
Black:	male	2
	female	2

3. RISK FACTORS AND PAST HISTORY

FACTOR	ABSENT	PRESENT	% PRESENT
Angina	113	68	37.6
Previous MI	148	33	18.2
Previous IHD/Cardiac	90	91	50.3
Hypertension	94	87	48.1
Diabetes Mellitus	146	35	19.3
Hypercholesterolaemia	159	22	12.2
Cardiac Failure	177	4	2.2
Peripheral vascular disease	166	15	8.3
Family History	103	78	43.1
Smoking	64	117	64.6
Alcohol	169	12	6.6
Prior aspirin use	154	27	14.9
Prior beta-blocker use	138	43	23.8

Subanalysis of risk factors:

Smoking: Females 33 (51.6%)

(p=0.0065)

Males 84 (71.8%)

Age: Smokers <70 years versus ≥ 70 years (p<0.0001)

4. PRESENTATION: TIME DURATIONS (for NQMI patients in 1993)

	All patients	Males	Females	Signi-ficance
Angina (duration prior to NQMI)	2.1 ± 2.5 weeks	1.99 ± 2.75	2.5 ± 2.1	(p=NS)
Chest pain (of acute NQMI)	4.0 ± 3.6 hours	4.13 ± 3.98	3.77 ± 2.8	(p=NS)
Time from pain onset to hospital	7.11 ± 8.8 hours	8.25 ± 10.4	4.73 ± 3.3	(p=NS)

5. CLINICAL FINDINGS (at primary admission with NQMI)

CPK

Mean = 872 I.U. (no significant difference between group with thrombolytics versus group without)
Range = 200-6961
Median = 688

Cholesterol

Mean = 6.5 ± 1.5 mmol/l
Range = 2.9 - 12
Median = 6.4

MB Fraction result only available in 13.

BP average: 100.3 ± 10.1 mmHg

hypotension in 8 patients

hypertension in 48 patients

ECG:

ST segment elevation	= 97	53.6% of total
ST segment depression	= 52	28.7%
T inversion (excluding ST segment elevation)	= 62	34.3%
ST segment depression (excluding T inversion)	= 11	6.1%

6. NQMI LOCALISATION BY ECG

Location	No.	%	Territory/Group	No.	%
Inferior	36	19.9			
Inferoposterior	5	2.8	Inferior	62	34.3
Inferolateral	21	11.6			
Posterior	3	1.7	Posterior	3	1.7
Anterior	15	8.3			
Anteroseptal	19	10.5	Anterior	72	39.8
Anterolateral	38	21.0			
Lateral	4	2.2	Lateral	4	2.2
Left BBB	4*	2.2			
Widespread ST-depression "subendocardial"	8	4.4	Non-localised	4	22.1
Unknown	28	15.5			
Therefore:	Localised	141	77.9%		
	Non-localised	40	22.1%		

* For purpose of analysis these are usually considered as indeterminate MI and are excluded from the rest of NQMI.

7. MANAGEMENT

Thrombolysis:

Total Number: 29 = 16% - Streptokinase 28
- TPA 1

	Number Thrombolysed	Total annual NQMI	Percent Thrombolysed
1990:	3	32	9.4
1991:	5	43	11.4
1992:	8	52	15.4
1993:	13	54	24.1

Nil 152

Thrombolysis use:

Amongst inferior infarct group = $^{14}/_{80}$ = 17.5%

Amongst anterior infarct group = $^{15}/_{72}$ = 20.8%

Amongst posterior infarct group = $^{0}/_{12}$ = 0%

(Amongst non-localised infarct group = 0%)

Heparin:

Given in 161 = 89.0%
Not given 20

Inotropes:

Given in 7 = 3.9%
Not given in 174

Beta-blockers:

Given in 127 = 70.2%
Not given in 54

Aspirin:

Given in 154 = 85.1%
Not given in 27

8. INVESTIGATIONS

A. CATHETERISATION

A1. REQUIREMENTS:

Early catheterisation:
- Yes 93 patients; cath. rate = 51.4%
- No 88

Late catheterisation: 28 patients (of these, 12 were repeats) (cath. rate = 16.1%)

Total catheterisation:
- Yes 109; cath. rate = 60%
- No 72

a) Indications for early catheterisation:

NQ	24
ECG	4
NQ plus "ischaemic-looking" ECG	19
EST positive	4
UAP history	12
Unstable / ongoing pain	20
UAP - post infarct angina	9
? Dissection	1

b) Catheterisation contra-indications

(i.e. catheterisation indicated for cardiac ischaemia/NQMI reasons, but poor lung function, morbid obesity, bedridden, poor LV/CMO, CVA):

Medical reason	15
Patient refused	4

c) Catheterisation complications: 3

Dissection of aorta	2
Ischaemic chest pain requiring IABP	1

d) **Early catheterisation requirements by ECG determined NQMI location/territory:**

NQMI locations	No cath	Cath	Cath %	Territory/Group %
Inferior	23	10	30.3	┐
Inferoposterior	5	19	79.2	├── 42.9
Inferolateral	12	1	7.7	┘
Posterior	2	10	83.3	
Anterior	12	31	72.1	┐
Anteroseptal	2	1	33.3	├── 55.6
Anterolateral	18	8	30.8	┘
Lateral	1	0	0	
Non-localised	13	3	18.8	
(No significant differences between no catheterisation and catheterisation, except for posterior infarcts p=0.012)				

A2. CATHETERISATION FINDINGS:

LVEDP mean = 22 ± 8.1mmHg
(Using one-way analysis of variance, the only factor achieving statistical significance with regard to elevation of LVEDP is CPK >500 : p=0.004)

A3. ANGIOGRAPHIC FINDINGS

a) **LV angiography**

		NO	YES	%
i)	**LV impaired**	15	86	85
ii)	**LV dilated**	97	4	4
iii)	**LV regional wall motion abnormality:**			
	- No abnormality	17		
	- Hypokinesia / Akinesia	74		
	- Dyskinesia	6		
	- Aneurysm	4*		

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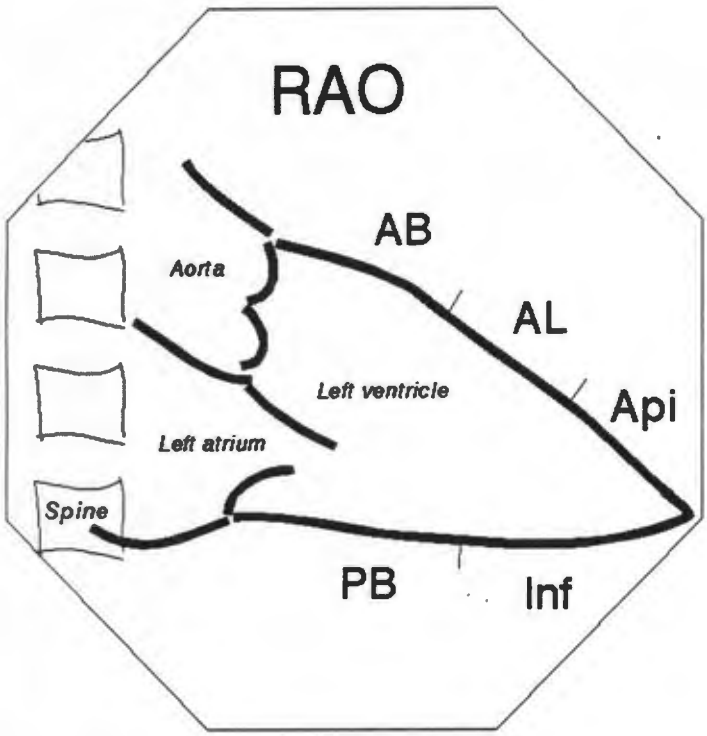
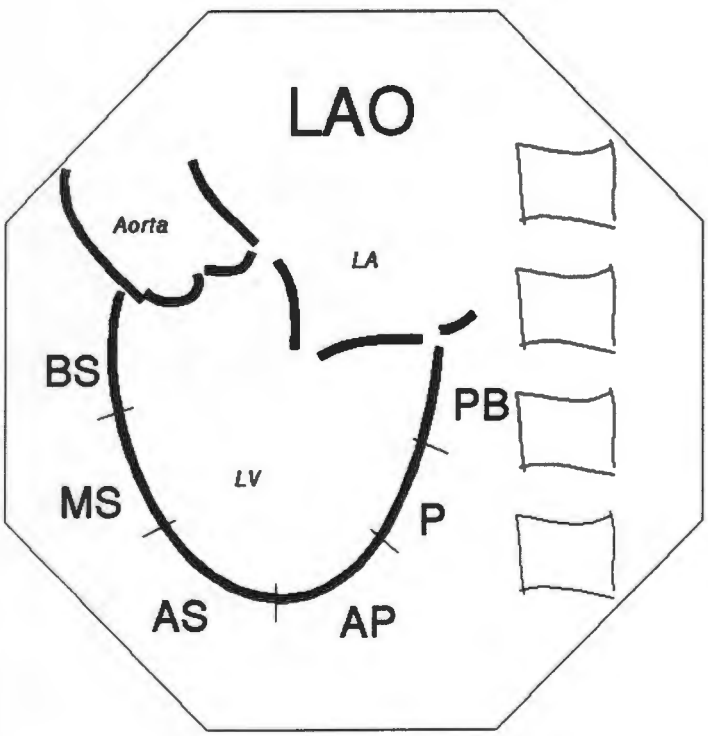
* All four had had previous MI.

LV ANGIOGRAPHY

SITES OF REGIONAL WALL MOTION ABNORMALITY





RAO and LAO projections:

1	Apical	= Api
2	Anterolateral	= AL
3	Anterobasal	= AB
4	Inferior	= Inf
5	Posterobasal	= PB
6	Basalseptal	= BS
7	Midseptal	= MS
8	Anteroseptal	= AS
9	Posterior	= P
10	Apicoposterior	= AP

Figure No.8: Sites of regional wall motion abnormality as defined by right anterior oblique (RAO) and left anterior oblique (LAO) projections in left ventricular (LV) angiography.

iv) LV site of wall motion abnormality:

LV site	No. of patients	Site combinations	No. of patients
1. Apical	6	4+5	14
2. Anterolateral	1	4+5+9	7
3. Anterobasal	0	4+9	3
4. Inferior	4	5+9	5
5. Posterobasal	10	1+4+5	4
6. Basalseptal	0	1+8	10
7. Midseptal	0	4+10	3
8. Anteroseptal	1	4+10+1	3
9. Posterior	3	1+2	8
10. Apicoposterior	0		
Undetermined	17		
		1+2+3+5	1
		1+2+8	3

v) NQMI localisation by angiography:

Inferior	16
Infero-posterior	35
Posterior	4
Anterior	33
Anterolateral	7
Undetermined	2

b) <u>Coronary angiography</u>

i) Coronary occlusion:

(i.e. some vessels occluded, whether or not culprit lesions are occluded or patent)

Occlusive C.A.D.	60	=	58.3%
Patent coronaries	43	=	41.7%

ii) Coronary artery disease by vessels:

Single vessel disease	28
Double vessel disease	24
Triple vessel disease	41
Mainstem ± other disease	9
Vasospasm	

(No risk factors e.g. DM, smoking, hypertension were identified for number of vessels involved.)

iii) Culprit vessels (infarct-related artery):

	Primary culprit lesion	**Secondary culprit**
Circumflex	25	7
Diagonal	1	1
LAD	31	8
Mainstem	2	2
Obtuse marginal	11	2
Right Coronary	28	6
Ramus	4	0

iv) Culprit vessel occlusion versus time of angiography:

	Early angiography	**Late angiography**	
Occluded	56 (60.2%)	9 (32.1%)	p=0.009)
Patent	37	19	

v) Collaterals:

None	39	39.8%
Grade 1	14	14.3% ┐
Grade 2	26	26.5% ├ 60.2%
Grade 3	19	19.4% ┘

vi) Culprit vessels per NQMI location:

Culprit	**Posterior NQMI**	**Posterior + Inferopost**	**Inferior NQMI**
Circumflex	8	21	15
Obtuse marginal	3	7	6
Right Coronary	1	15	22
Ramus	0	1	1

B. **OTHER INVESTIGATIONS**

Exercise stress tests: Total 9
Positive 6

9. FINAL LOCALISATION OF NQMI

NQMI location was determined by these factors, where available, which are listed in decreasing order of certainty or validity with regard to power of localisation:

* LV angiography - regional wall motion abnormality.
* Echocardiographic findings
* Nuclear imaging
* ECG - ST Segment elevation
* Coronary angiography - supposed culprit vessel
* ECG - T wave inversion
* ECG - ST depression and T wave inversion combination

NQMI Location	No.	%	Group/Territory	No.	%
Inferior	33	18.2			
Inferoposterior	34	18.8	Inferior	80	44.2
Inferolateral	13	7.2			
Posterior	12	6.6	Posterior	12	6.6
Anterior	43	23.8			
Anteroseptal	3	1.7	Anterior	72	39.8
Anterolateral	26	14.4			
Lateral	1	0.6	Lateral	1	0.6
Non-localisable	16	8.8	Non-localisable	16	8.8

10. ACTIVE MANAGEMENT AND RECOMMENDATIONS

A. RECOMMENDATIONS

a) Early Catheterisation (n=93) Recommendation/Action:

Primary Action			Alternative action (eg if recurrence of symptoms)	
Medical treatment	43	———	PTCA	7
			CABG	5
PTCA	13	———	CABG	1
CABG	37			

b) Late catheterisation (28):

Medical*	15	———	PTCA	3
			CABG	0
PTCA	7	———	CABG	2
CABG	6			

B. REVASCULARISATION PROCEDURES

TOTAL = 63 patients.

PTCA	**Early**	**Late**	
Total	13	7	
Successful	11	5	p=NS
CABG			
Number	39	8	

---

* Five of the 15 were considered inoperable.

Revascularisation versus gender:

	Early revascularisation		**Late revascularisation**		**TOTAL**
	PTCA	CABG	PTCA	CABG	
Female	2	8	0	2	12
					p<0.001
Male	9	31	5	6	51

PTCA (rate: 11.0%) — Early - 13; Late - 8

CABG (rate: 26.0%) — Early - 39; Late - 7

11. EPIDEMIOLOGICAL TESTS ANALYSING ECG VERSUS ANGIOGRAPHY IN LOCALISATION OF NQMI*

A. PREDICTIVE VALUE OF ECG

By grouped territories:

Inferior Group NQMI

		Angio: Inf. grp (39)	Angio: Other (not inf) (48)
ECG	Inf MI (23)	20 a	3 b
	Not inf MI (64)	19 c	45 d

Anterior Group NQMI

		Angio: Ant. grp (34)	Angio: Other (53)
ECG	Ant MI (38)	24	14
	Not ant MI (49)	10	39

Posterior Group NQMI

		Angio: Post grp (11)	Angio: Other (76)
ECG	Post MI (3)	2	1
	Not post MI (84)	9	75

Non-localised NQMI

		Angio: Un-determined (3)	Angio: Localised (84)
ECG	Non-localis. (16)	3	13
	Localised (71)	0	71

---

* First time MI; i.e. excluding previous MI.

B. EPIDEMIOLOGICAL TESTS: ECG VERSUS ANGIOGRAPHY

B1. ANALYSIS BY GROUPED TERRITORIES

	Inferior Group	Anterior Group	Posterior Group	Non-localised Group	Overall
Prevalence = (a+c)/(a+b+c+d)	44.8	39.1	12.6	3.4	
Sensitivity = a/(a+c)	51.3	70.6	18.2	100	56.3
Specificity = d/(b+d)	93.8	73.6	98.7	84.5	87.7*
False neg. rate = c/(a+c)	48.7	29.4	81.8	0	
False pos. rate = b/(b+d)	6.3	26.4	1.3	15.5	
Positive predictive value = a/ (a+b)	87.0	63.2	66.7	18.8	61.3**
Negative predictive value = d/(c+d)	70.3	79.6	89.3	100	
Overall accuracy = (a+d)/(a+b+c+d)	74.7	72.4	88.5	85.1	

B2. ANALYSIS OF SPECIFIC ECG LOCATION VERSUS ANGIOGRAPHY LOCATION:

	Inf.	Inf. post.	Inf. lat.	Post.	Ant.	Ant. sept.	Ant. lat.	Over-all
Sensitivity %	55	6.9	100	18.2	8	100	75	**25.3**
Positive predictive value	36	100	10	66.7	60	6	35	**29**

---

* Average specificity in localising NQMI within total NQMI and not NQMI versus non-NQMI.

** Or 69.7% if only considering localisable NQMI.

B3. ANALYSIS BY INFARCT AREA:

a) Posterior involvement (as determined by angiography)

Total = pure posterior MI + inferoposterior MI

46 = 12 + 34

ECG sensitivity in detecting posterior involvement = 11.4%,
but positive predictive value = 100%

b) ECG non-localisable group (where checked by angiography):

Of the total of 20 NQMI not localisable by ECG, location by angiography is:

- Inferior 3
- Inferoposterior 5
- Posterior 3
- Anterior 6
- Remain non-localised 3

c) ECG "subendocardial group": i.e. widespread ST segment depression:

Total 10

Angiographic NQMI location is scattered in all territorial groups.

C. EVALUATION OF COMPONENTS OF ECG RE: LOCALISATION OF NQMI

Tests evaluated the Positive Predictive value of the following specific components of the 12-lead ECG in NQMI (excluding previous MI and LBBB):

- ST segment elevation
- ST segment depression
- ST segment depression alone (excluding T inversion)
- T wave inversion (not associated with ST segment elevation)
- T wave inversion alone (excluding ST depression)

ECG	No.	Positive Predictive Value:				
		ST ↑	ST ↓	ST ↓ alone	T ↓	T ↓ alone
Inferior	23	100%	67%	50%	67%	50%
Anterior	38	72%	36%	50%	41%	50%
Overall		**79%**	**48%**	**50%**	**50%**	**50%**

12. FOLLOW-UP

	No.	Percent
Some follow-up available	176	97.2%
Lost to all follow-up	5	2.8%

Follow-up at 1 month	176	therefore rate is	97.2%
3 months	173		95.6%
12 months	166		91.7%

Range of follow-up:	0 - 62 months
Median follow-up time:	20 months
Average:	21.0 ± 12.3 months

13. OUTCOME

A. IMMEDIATE OUTCOME

Stable	141 patients	77.9%
Unstable	40 patients	22.1%

Unstable group:

Cardiovascular instability	= 23
Ongoing ischaemic chest pain	= 17
Arrhythmia (life-threatening) (e.g VF CHB with syncope)	= 3

Of the cardiovascular unstable group: IABP required in 4.

a) Immediate Outcome Subanalysis

i) Univariate:

Identifiable risk factors / factors associated with immediate outcome:

Factor	Stable patients	Un-stable	Odds ratio	95% Con-fidence limits	Signifi-cance
Diabetes Mel.	20	15	3.63	1.5-8.6	p=0.001
Alcohol use	12	0	0		p=0.043 *
Smoking**	97	20	0.45	0.21-0.98	p=0.03
Age >40 years	126	40		1.07-	p=0.02
Thrombolysis	27	2	0.22	0.02-0.96	p=0.03
ST segment depression	4	7	7.27	1.7 -35.4	p=0.003
"Subendo-cardial" on ECG	3	5	6.6	1.2-43.7	p=0.014

---

* Note: Alcohol use and smoking appear to confer a reduction in risk of instability.

** Mean age of non-smokers = 61.4 ± 2.4 years; mean age of smokers = 52.0 ± 1.8 years.

No significance was achieved for previous ischaemic heart disease, hypertension, cardiac failure, peripheral vascular disease, prior aspirin or beta-blocker use or ECG non-localisability. Analysis of catheterisation findings showed no significant differences in LVEDP, occlusive versus patent coronary artery disease, number of coronary arteries involved or culprit lesions.

ii) Multivariate analysis:

Discriminant analysis:

Factor	**Discriminant function coefficient (standardised)**
Diabetes Mellitus	0.668
Age	0.430
Alcohol use	-0.368
Smoking	-0.199
chi square = 19.1	significance level = 0.0007

Stepwise logistic regression analysis:

Factor	**Significance level**
Diabetes Mellitus	0.003
Age	0.03
Alcohol use	NS
Thrombolysis	NS
Smoking	NS

B. <u>LATE OUTCOME</u>

Cardiac failure after primary admission:

- Total number: 24 (excluding previous cardiac failure)

i) Univariate analysis of identifiable risk, predictive or associated factors for late outcome:

Factor	Odds Ratio	95% Limits	Signi-ficance
Use of inotropes	10	1.53-71.6	p=0.007
Unstable immediate outcome	3.95	1.46-10.69	p=0.002
Hypotension on admission	7.45	1.26-42.6	p=0.013
Inferior NQMI territory	0.25	0.05-0.92	p=0.022
Beta-blockers post event	0.27	0.10-0.71	p=0.002
Ischaemia recurrence ≤12 months	2.56	0.92-7.78	p=0.046

No significance was achieved for age, past history e.g. diabetes CPK level, thrombolysis, number of vessels involved, early revascularisation or early recurrence.

ii) Multivariate analysis:

Discriminant analysis:

Factor	Discriminant co-efficient (standardised)
Inotrope use	0.422
Unstable immediate outcome	0.424
Ischaemia recurrence ≤1 year	0.473
Beta-blockers post event	-0.437
chi square = 26.0	Significance level = 0.00003

Stepwise logistic regression analysis:

Factor	Co-efficient	Significance level	F-Ratio
Beta-blocker use possible	-0.167	0.0056	7.97
Inotrope use	0.326	0.018	5.70
Recurrence by 1 year	0.105	0.04	4.16

14. MORTALITY

A. TOTALS

	Early In-hospital	≤3 months	≤12 months	Total Follow-up period
Total deaths	2	9	16	32
Cardiac deaths	2	7	13	23
Non-cardiac deaths	0	2	3	9

B. CAUSES OF DEATH (Breakdown):

Cardiac deaths (n=23)
- 0 Early in-hospital (non-peri-operative) deaths
- 2 Intra/peri-operative deaths (day 0 + day 1)
- 21 Cardiac causes (recurrence ischaemia, CF)

Non-cardiac deaths (n=9)
- 3 CVA
- 1 Pulmonary embolism
- 2 Cancer
- 1 Diabetes Mellitus
- 1 Pneumonia
- 1 Unknown

C. MORTALITY RATES (Versus number of patients followed-up at particular time)

a) Total Deaths:

Overall mortality rate	= $^{32}/_{181}$	=	17.7% (with follow-up to 62 months)
Three months	= $^{9}/_{173}$	=	5.2%
One-year mortality rate	= $^{16}/_{166}$	=	9.6% (with a 92% follow-up rate)

b) Cardiac Deaths:

Early in-hospital,	= 0	=	0%
but if 2 peri-operative deaths are included:	= $^{2}/_{181}$	=	1.1%
One month	= $^{4}/_{176}$	=	2.3%
Three months	= $^{7}/_{173}$	=	4.0%
One year	= $^{13}/_{166}$	=	7.8%
Overall	= $^{23}/_{181}$	=	12.7%

NQMI: SURVIVAL

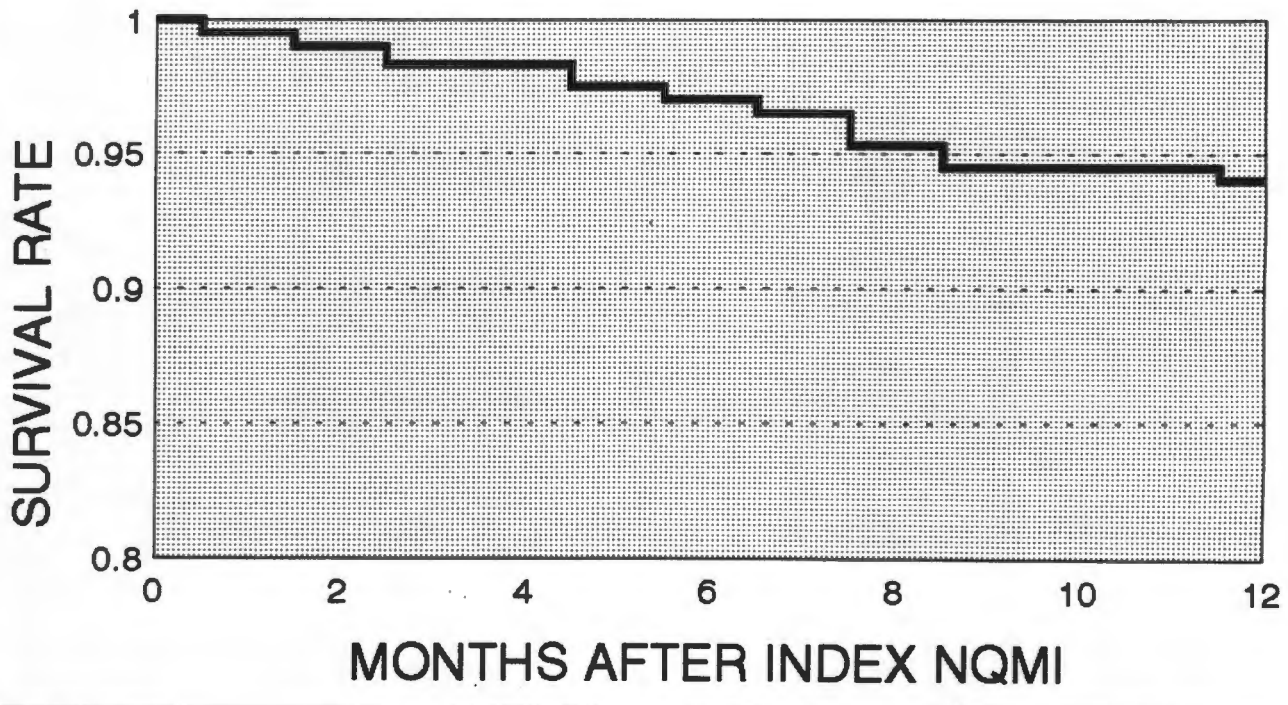


Figure No.9: Kaplan-Meier plot of survival probabilities for the total group of GSH-study patients in the first year after NQMI.

D. MORTALITY SUBANALYSIS

a) Univariate:

Risk/assoc. Factors:	Total Cardiac Deaths			Cardiac Deaths at 12 months		
	Odds Ratio (OR)	95% Confidence limits	Significance	OR	95% limits	Significance
PMH: Ischaemia	2.7	(0.97-8.21)	p=0.035			NS
Diabetes Mellitus	3.38	(1.14-9.52)	p=0.01	5.47	(1.27-24.09)	p=0.01
CF		(4.53-α)	p=0.0003	44.7	(3.06-2360)	p=0.0015
PVD	5.44	(1.21-22.1)	p=0.013			NS
Age			p=0.003			NS
Hypotension	5.25	(0.71-33.06)	p=0.05	8.7	(1.15-51.45)	p=0.01
Hypercholesterol			p=0.04			NS
Unstable immediate outcome	4.36	(1.54-12.1)	p=0.002	4.87	(1.28-18.75)	p=0.009
Cath. early			NS	0.19	(0.02-0.97)	p=0.02
Cath. Triple VD	8.57	(1.01-394)	p=0.028			p=0.046
Culprits: LAD/main			NS	9.85	(0.89-492)	p=0.014
Collaterals present			NS			
B.-blockers	0.24	(0.09-0.65)	p=0.001	0.29	(0.08-1.09)	p=0.035

D. **MORTALITY SUBANALYSIS** - Univariate/cont....

Risk/assoc. Factors:	Total Cardiac Deaths			Cardiac Deaths at 12 months		
	Odds Ratio (OR)	95% Confidence limits	Significance	OR	95% limits	Significance
Recurrence:						
Early (≤ 3 months)	3.67	(1.08-14.15)	p=0.018*	4.57	(1.08-22.18)	p=0.019
Twelve mnths			NS			NS
Total			NS			
Re-admission:						
Early (≤ three months	2.62	(0.86-7.46)	p=0.048	6.87	(1.57-30.6)	p=0.004**
Total			NS			NS

Univariate analysis shows no significance as risk factors:

gender, race, past history of angina, myocardial infarction, hypertension, hypercholesterolaemia, alcohol, smoking, family history, aspirin use, CPK value, ECG ST segment elevation or depression, thrombolysis, heparin use, inotrope use, catheterisation findings of occlusive coronary artery disease and NQMI localisation/non-localisation or specific territory group.

Survival benefits by twelve months:

Early catheterisation	p=0.02
PTCA	p=NS
CABG	p=NS

---

* Nine of the 10 cardiac deaths (excluding the 2 intra-operative deaths) have a median recurrence of 2 months.

** Remain significant even when excluding - previous myocardial infarct
- thrombolysis
- revascularisation procedures

b) **Multivariate analysis**

i) Discriminant analysis of the following factors as risk factors for cardiac deaths at 12 months, showed:

Factor	Discriminant function coefficient (standardised)
Re-admission by 3 months	0.628
Past history of cardiac failure	0.833
Hypotension on admission	0.406
Immediate outcome	0.296
with chi square = 53.7 and predicted groups:	no deaths = 94.59% deaths = 53.85%

ii) Stepwise logistic regression analysis - analysing cardiac mortality at 12 months as the dependent variable:

Factor	Significance level	F-ratio
Previous cardiac failure	0.00001	37.35
Hypotension on admission	0.0008	11.7
Re-admission by 3 months	0.0012	10.9
Early outcome		3.72
Recurrence by 3 months		0.80
Beta-blockers		0.244
Diabetes		0.128
Early catheterisation		0.01

15. RECURRENCE OF ISCHAEMIA

Recurrence of ischaemia is divided into:

1) Recurrence of symptomatic ischaemia (refers to earliest symptomatic recurrence i.e. of myocardial ischaemia) (equivalent to event rate)
2) Recurrence requiring admission
3) Reinfarction

A. RECURRENCE: median - 3 months
range - 0.1-37 months

Rates (versus patients followed up)	at 3 months	at 12 months	Total follow-up period
Recurrence	$^{53}/_{173}$ = 30.6%	$^{85}/_{166}$ = 51.2%	$^{103}/_{174}$ = 59.2%
Re-admission	$^{33}/_{173}$ = 19.1%	$^{49}/_{166}$ = 29.5%	$^{60}/_{174}$ = 34.5%
Reinfarct	$^{5}/_{173}$ = 2.9%	$^{15}/_{166}$ = 9.0%	$^{25}/_{174}$ = 14.4%

B) PROPORTION OF ONE-YEAR OCCURRENCES VERSUS TIME:

	Recurrence by 12 months (85)	Re-admission (49)	Reinfarct (15)
At 1 month	$^{39}/_{85}$ = 45.9%	$^{27}/_{49}$ = 55.1%	$^{4}/_{15}$ = 26.7%
At 2 months	$^{47}/_{85}$ = 55.3%	$^{32}/_{49}$ = 65.3%	$^{5}/_{15}$ = 33.3%
At 3 months	$^{53}/_{85}$ = 62.4%	$^{33}/_{49}$ = 67.3%	$^{5}/_{15}$ = 33.3%

C) SURVIVAL WITHOUT SIGNIFICANT MORBIDITY:

Three-month survival	$^{114}/_{173}$	=	66%
Twelve-month survival	$^{76}/_{166}$	=	46%

NQMI: MONTHLY RATE OF RECURRENCE OF ISCHAEMIA

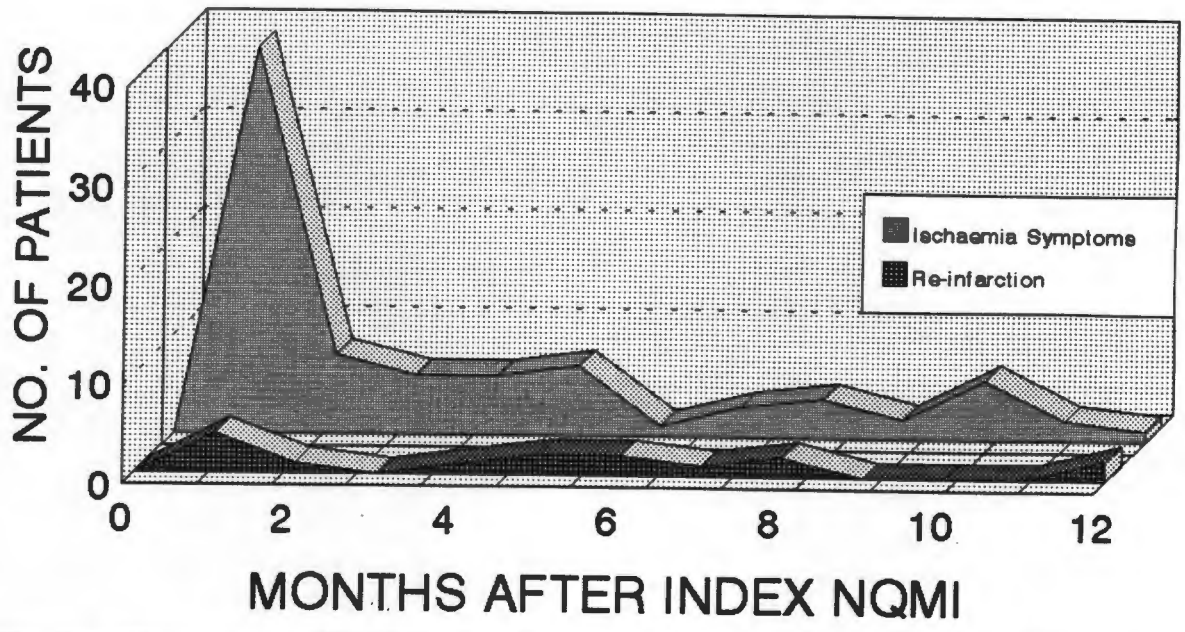


Figure No.10: Monthly rates of first symptomatic recurrence of ischaemia and of re-infarction after the index NQMI.

D. SUBANALYSIS OF RECURRENCE OF ISCHAEMIA - RISK FACTORS

a) Univariate analysis (single factor study)

i) Early symptomatic recurrence (i.e. ≤3 months)

Risk or Associated Factors	Odds Ratio	95% limits	Signif-cance
PMH Hypertension	2.06	1.02-4.22	p=0.03
PMH Hyperchol	2.88	1.02-8.14	p=0.02
CPK >440*	0.49	0.24-1.03	p=0.04
Thrombolysis	2.9	1.07-7.8	p=0.016
Early Cath i.e. active management	0.51	0.25-1.03	p=0.04
Early revascularisation	0.09	0.01-0.37	p=0.0001
Location of NQMI (inferior MI)	0.50	0.24-1.04	p=0.047**
Aspirin use	0.37	0.15-0.96	p=0.02

---

* **CPK:**

	no recurrence	**recurrence ischaemia ≤ 3 months**
mean	957.2	691.4
median	759.5	489

** All risk factors maintain significance if pathological R wave infarcts are excluded (i.e. posterior-infarction on ECG) except inferior location of NQMI.

Risk or Associated Factors for Early Recurrence cont/....						
Excluding early revascularisation				Excluding Thrombolytic		
	OR	95%	Signifi-cance	Odds Ratio	95%	Signifi-cance
PMH Hypertension				2.28	1.02-5.21	p=0.029
PMH Hyperchol				2.78	0.91-8.34	p=0.036
CPK > 440	0.36	(0.15-0)	0.015	0.39	0.17-0.90	p=0.03
Early revasc.				0.10	0.01-0.44	p=0.0006
Location of NQMI				0.39	0.16-0.90	p=0.016
(inferior MI)						
Aspirin use				0.37	0.14-1.02	p=0.026

ii) Recurrence (symptomatic) by 12 months:

Factor	OR	95% limits	Significance
Thrombolysis	3.25	(1.13-10.59)	p=0.015
Early cath	0.32	(0.16-0.62)	p=0.0003
Early revascularisation	0.12	(0.04-0.31)	p=0.0001
Smoking	0.28	(0.08-0.89)	p=0.016
Inferior location of NQMI	0.47	(0.24-0.92)	p=0.016

Analysis for the following factors revealed no significance:

gender, age, previous angina, previous myocardial infarct, diabetes mellitus, previous cardiac failure, alcohol, family history, prior aspirin use, hypertension on admission, hypercholesterolaemia as measured on admission, use of heparin, use of inotropes, acute outcome, ECG changes: ST segment elevation versus depression versus T inversion, cath findings: number of vessels involved, culprit vessel, occlusive or patent coronary artery disease, presence or absence of collaterals, non-localisation or localisation of NQMI except the inferior group.

b) **Multivariate analysis for recurrence by 3 months:**

i) **Stepwise logistic regression:**

Factor	Significance	F-Ratio
Early revascularisation	0.0003	13.46
PMH hypercholesterolaemia	0.017	5.83
Thrombolysis	0.02	3.51
Aspirin	0.037	4.41
Inferior infarction	0.04*	4.10
CPK	0.045	4.07

ii) **Discriminant analysis for risk factors for recurrence by 3 months:**

Factor	Discriminant function co-efficient (standardised)
Early revascularisation	-0.60
Thrombolysis	0.45
PMH Hypercholesterolaemia	0.38
Aspirin	-0.37
Inferior infarct	-0.32
History of hypertension	0.23
Early catheterisation	0.12
CPK level	-0.30
Chi square = 41.5 Predicted group percentages: for recurrence = 75.5% for non-recurrence = 70.0%	

* Significance increases to 0.0197 if infero-lateral and infero-posterior infarcts are excluded.

c) **Multivariate analysis for recurrence by 12 months**

i) **Stepwise logistic regression:**

Factor	Significance	F-Ratio
Early revascularisation	0.00	38.34
Inferior infarction	0.00**	5.66
Thrombolysis	0.019	3.08

ii) **Discriminant analysis**

Factor	Discriminant co-efficient (standardised)
Early revascularisation	-0.866
Thrombolysis	+0.285
Inferior infarct	-0.396
Chi square = 44.7 Predicted group percentages: for recurrence by 12 months = 77.6% for non- recurrence = 60.7%	

E. **REINFARCTION BY 12 MONTHS: SUBANALYSIS**

i) **Univariate analysis:**

Risk/Associated Factors	Odds Ratio	95% Confidence Limits	Significance
Recurrence by 3 months	3.04	0.93-10.07	p=0.04
Re-admission by 3 months	3.68	0.97-12.79	p=0.028
Early Catheterisation	0.05	0-0.38	p=0.0003
Inferior NQMI	0.29	0.05-1.12	p=0.046

No other significant associations with reinfarction were noted including age and past medical history.

** Significance decreases to 0.0045 if infero-lateral and infero-posterior infarcts are excluded.

16. EARLY CONSERVATIVE TREATMENT VERSUS ACTIVE INTERVENTION

A. Analysis comparing initial **conservative treatment** (no early catheterisation, n=88) **versus active intervention** (catheterisation and appropriate action during the primary admission, n=93). (No statistically significant differences are noted in demographics of both groups, nor in NQMI location.)

a) Recurrence

	Conservative (82)*	Active (92)*	OR	95% Limits	Signifi-cance
Early (≤ 3 months)	$^{31}/_{82}$**	$^{22}/_{92}$	0.52	(0.25-1.05)	p=0.047
By 12 months	51	34	0.36	(0.18-0.69)	p=0.0009***
Total period of F/U	58	45	0.40	(0.20-0.78)	p=0.0035***

b) Re-admission

By 3 months	21	12	0.43	(0.18-1.00)	p=0.03
By 12 months	34	15	0.12	(0.26-0.55)	p=0.0001***
Total	38	22	0.36	(0.18-0.73)	p=0.0019***

c) Reinfarction

By 3 months	5	0	0	(0-0.97)	p=0.018
By 12 months	14	1	0.05	(0-0.38)	p=0.0002***
Total	18	7	0.32	(0.11-0.86)	p=0.012***

d) Cardiac Failure NS

---

* These are unlike totals because only patients with follow-up were compared statistically.

** Denominators vary because all statistical analysis takes into account the number of patients followed up to a particular time.

*** Significance is maintained even when excluding thrombolysis, LBBB and/or previous myocardial infarction.

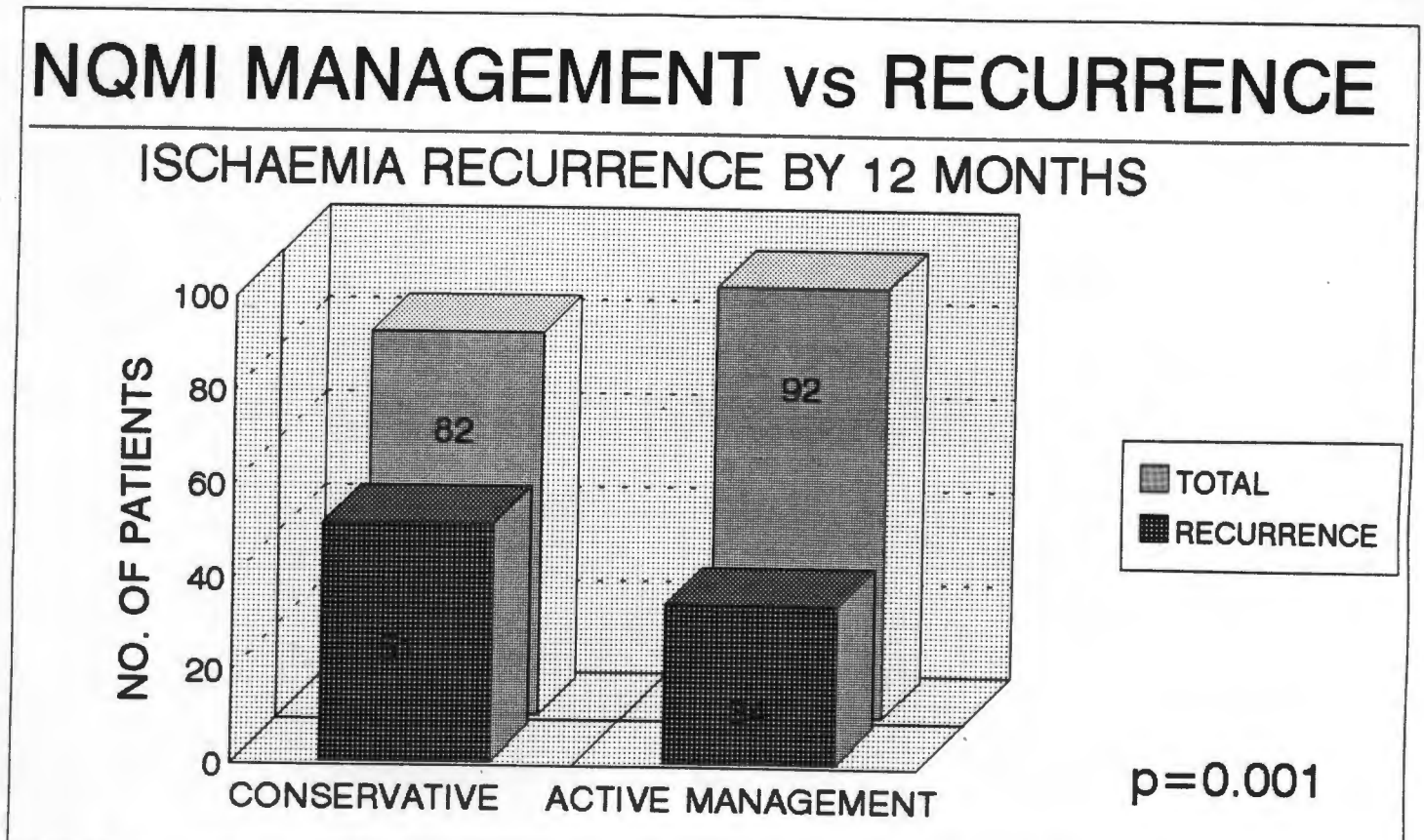


Figure No.11: Recurrence of symptomatic ischaemia in the first year in patients who were managed conservatively versus actively investigated early i.e. during the primary admission.

e) **Mortality**

Cardiac deaths	15	8			p=0.055
Total deaths	21	11	0.41	(0.17-0.97)	p=0.025

Note: Of patients who underwent early catheterisation for reasons other than NQMI alone, 41 of the 69 were recommended to have revascularisation.

B. **Comparison: no early catheterisation (n=88) versus early catheterisation for NQMI only (n=24).**

No statistically significant differences between the two groups were present with respect to:

- demographic factors
  (except age: no early cath : mean age = 57.3 years
  early cath for NQMI : mean age = 48.5 years
  (p=0.0005)
- use of thrombolytics
- previous myocardial infarction
- NQMI localisation
- CPK levels

a) **Recurrence:**

	No early cath. (82*)	Early cath. for NQMI (23*)	OR	95% limits	Signifi-cance
Within 3 months	31	7			NS
Within 12 months	51	11			NS

b) **Re-admission:**

≤ 3 months	21	4			NS
≤ 12 months	34	4	0.27	(0.06-0.94)	p=0.023**

c) **Reinfarction:**

≤ 3 months	5	0			NS
≤ 12 months	14	0	0.00	(0.00-0.26)	p=0.0001

d) **Mortality:**

Cardiac deaths	15	2			NS

* Number of patients with follow-up.
** Only this factor maintains significance when the age factor is neutralised p=0.049.

17. SUBGROUP ANALYSIS

a) **"Subendocardial group" / widespread ST segment depression on ECG:**

Compared to the other NQMI groups localised by ECG, there are no significant differences with respect to demographic or risk factors except:

Diabetes mellitus which approaches significance (p=0.046)

Immediate outcome is worse (p=0.014)

No specific angiographic findings were noted.

b) **Mainstem lesions on angiography:**

Number = 4

Immediate outcome: all 4 unstable - 2 with cardiovascular instability
- 2 with ongoing pain

c) **ECG non-localisable group that underwent angiography (20):**

Final location:		
	Undetermined	3
	Inferior	3
	Infero-posterior	5
	Posterior	3
	Anterior	6

No significant increase in recurrence in non-localisable group.

d) **Subgroup analysis: Angiographic Findings:**

No correlation was established between occlusive or patent coronary artery disease and specific ECG changes: ST segment elevation / depression or T inversion.

Collaterals were found more frequently in groups which had previous ischaemic heart disease (p=0.016).

e) **Subgroup analysis: Mortality:**

Beta-blockers:

Prior use of beta-blockers before the index NQMI, did not significantly influence the outcome or subsequent mortality.

However, beta-blocker use after the index NQMI was associated with a reduction in:

	Significance	Odds Ratio	95% Limits
Total mortality	p=0.0001	OR 0.21	10.09-0.50
Cardiac mortality	p=0.001	OR 0.24	0.90-0.65
Cardiac mortality at 12 months	p=0.035	OR 0.29	0.08-1.09

There was a significant difference in use of beta-blocker between the stable and unstable immediate outcome groups (112/141 versus 15/40 p=0.0001)

In the stable outcome group, there was no significant reduction in mortality amongst those on beta-blockers. However, total mortality was significantly less in the group of unstable outcome patients on beta-blockers (p=0.014) (OR 0.14 : 0.01-0.87).

DISCUSSION

DISCUSSION

1. RESULTS

A. STUDY PRIMARY ENDPOINTS

B. GENERAL RESULTS

1A. STUDY PRIMARY ENDPOINTS

1) Outcome

a) Immediate Outcome

As defined previously, the immediate course and status during the first 24-48 hours of admission to the CCU were assessed and classified as stable or unstable. The unstable group could have been considered to have required intensive care management and intervention for subsequent survival. In addition, it was important to assess whether early instability was a marker for a subsequent unfavourable outcome with increased mortality or recurrence of ischaemia. If this were the case, then identifiable risk factors of poor immediate outcome could possibly identify those patients requiring earlier or more active intervention.

Of the study patients, 77.9% (141 patients) were stable (Figure No. 12). Of the 22.1% (40 patients) whose immediate course and outcome of acute myocardial infarction was unstable, 23 patients were cardiovascularly unstable (haemodynamically unstable, in pulmonary oedema or requiring inotropes), 17 had ongoing chest pain and 3 had life-threatening arrhythmias. Four required intra-aortic balloon pumping (IABP). Inotropes were only required in 3.9% of the

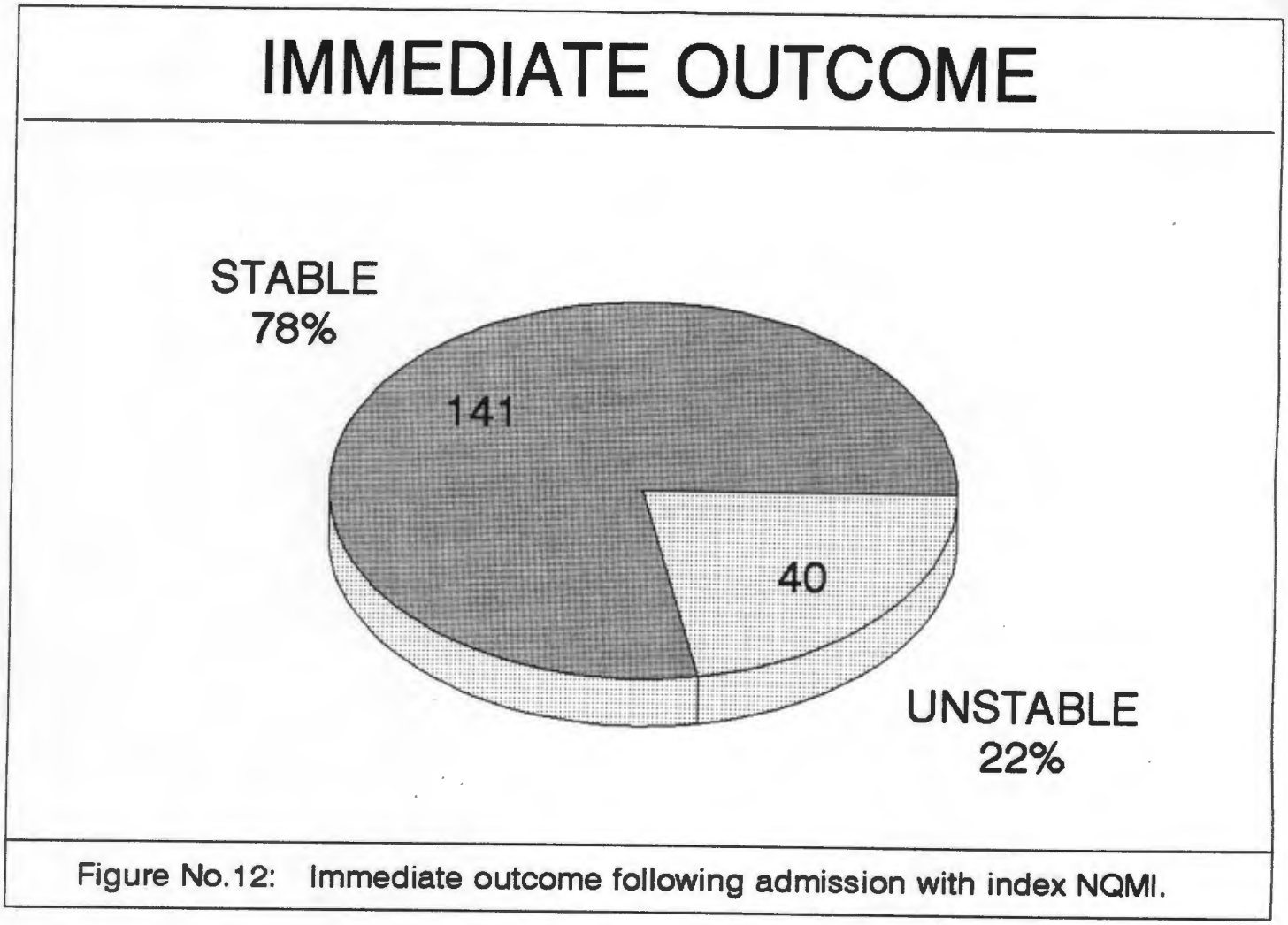


Figure No.12: Immediate outcome following admission with index NQMI.

patients. Interestingly, none of these unstable patients died except for two who died intra- or immediately post-coronary artery bypass graft surgery (CABG). This relatively good immediate outcome is a credit to the CCU and is also in keeping with the better immediate course normally found in NQMI. Goldberg in the Worcester Study showed a significantly lower complication rate in the acute phase in NQMI as opposed to QMI: 19% of patients had hypotension, 3% shock and 2.2% had life-threatening arrhythmias.(54)

In this GSH study, the 17 patients with ongoing ischaemic chest pain were included in the unstable group. Other studies of NQMI have defined those patients with recurring chest pain more specifically as either infarct extension or reinfarction,

which have been regarded as evidence of treatment failure. The group of unstable patients in this study with ongoing pain, was considered to be part of the spectrum of presentation of all infarcts, not as treatment failure. Rather, it was an indication for urgent active intervention. Re-elevation of CPK enzyme levels, in order to confirm extension or recurrence of infarction, was not specifically sought in this group, unless the ECG suggested ST segment elevation or development of Q waves.

Univariate analysis determined that diabetes mellitus, age >40 years and widespread ST segment depression on admission ECG were probable positive risk factors. That diabetes mellitus and increasing age are risk factors, is not surprising as both are associated with increased prevalence of multivessel coronary artery disease and previous myocardial ischaemia which itself did not achieve any statistical significance as a risk factor.

Maeda, in analysing the different clinical implications of ST depression and T inversion in 42 NQMI patients on the basis of ECG, coronary angiography and left ventriculography, suggested that, unlike T wave inversion which was frequently preceded by ST segment elevation and represented a recovery phase in a localised infarct within presumed one-vessel territory, ST segment depression indicated the presence of extensive ischaemia in the subendocardium of multivessel territories.[70] In the GSH study, ST segment depression was associated with the presence of multivessel disease on angiography ($p=0.045$), and although it was shown to be

statistically linked to poor immediate outcome, it did not predict for subsequent increased mortality or recurrence of ischaemia.

Further review of analysis of risk factors for immediate outcome showed that smoking, alcohol and use of thrombolytics were 'negative' risks. The effect of smoking, at face value, is surprising. However, it is known that smokers who survive MI, frequently have a better outcome[134][135] (see discussion under smoking). Thrombolytics, by saving myocardium, would be expected to improve the immediate outcome of patients if compared to QMI patients, provided no complications from thrombolysis itself occurred. That thrombolytics appear to be associated with lower risk of immediate complications in the group of patients with NQMI, may be because of the strict criteria required for thrombolytic administration - particularly ST segment elevation. This therefore, excludes the group of patients with ST segment depression, which as noted, is associated with poor immediate outcome.

Multivariate analysis confirmed that diabetes mellitus is a significant independent risk factor for immediate outcome.

Comparison of immediate outcome with other studies is difficult. In the TIMI II Study, a combination of both various patient characteristics and also unfavourable findings after admission defined patients as being "not low risk" e.g. ≥70 years, anterior MI, crackles $>^{1}/_{3}$ of lung fields, systemic hypotension with sinus tachycardia, atrial flutter or

fibrillation, pulmonary oedema and cardiogenic shock. Thus, 56% of NQMI patients were considered to be "not low risk".[22]

A similar combination performed in this study revealed 51% (93) to be in a similar group.

The two patients who died were undergoing emergency CABG. One did not come of bypass and the other died within hours of the operation. In both cases, surgery was performed following active investigation during the primary CCU admission. These were the only deaths among the 47 patients in total who had CABG (39 as a result of investigation during the primary admission and 8 following recurrence of ischaemia requiring active intervention). The CABG rate was therefore, 26%. The operative mortality rate was 4.3% and was related to emergency CABG procedures. These results compare well with other centres. Madigan et al reported a prospective study of 28 patients treated with CABG within 3 months of NQMI with a 3.6% incidence of peri-operative death and a 10.7% incidence of peri-operative acute myocardial infarction.[128] Furthermore, it is known that emergency procedures are associated with higher mortality.

b) <u>Late outcome - cardiac failure</u>

Excluding those who had a previous history of cardiac failure, 24 patients were noted to develop cardiac failure during the total follow-up period. This cardiac failure rate of 13.6% compares favourably with the prognosis assessment in the Framingham Heart Study which showed an incidence of cardiac

failure following NQMI of 10.1% and 15.1% at 1 and 5 years respectively[10].

The development of late cardiac failure was statistically associated with an unstable immediate outcome and the use of inotropes during the primary admission. Recurrence of ischaemia within 12 months was also related. Surprisingly, no statistical significance could be achieved for past history of myocardial infarction/ischaemia.

NQMI located inferiorly and also the use of beta-blockers after the index event, both correlated negatively with subsequent cardiac failure. However, it was only the beta-blocker use that maintained significance following multivariate analysis. As the introduction of beta-blockers was considered routine practice, intolerance or failure of their use probably marked those patients with poorer left ventricular function (which was the most likely mechanism of the cardiac failure)[34].

Cardiac failure after the index NQMI, itself, may be a predictor of mortality as 9 of these 24 patients died; a significantly higher proportion than those who did not develop failure ($p=0.005$) (OR = 4.23).

2) **Mortality**

Analysis and rates of mortality are traditionally divided into:

a) Early or in-hospital mortality; and

b) Subsequent or post-discharge mortality;

usually on the presumption that the former is related to the acute "peri-infarction-related complications" and the latter to the long-term effects of MI.

a) <u>In-hospital mortality</u>

In this study there were no in-hospital deaths except for two patients who underwent emergency coronary artery bypass grafting (CABG) surgery and died intra-operatively or within the first day, post-operatively.

Compared to generally published figures, this is remarkable. Although meta-analyses of in-hospital mortality rates give an average of 10% (with a range from 3-32%)[24], this is for all types of NQM-infarcts and includes some studies with extra-ordinarily high mortality rates. Select subsets of NQMI show different results, although the Worcester Heart Attack Study involving a large number of patients (2451) in one region in the USA, with or without previous infarcts, showed an in-hospital mortality rate for NQMI of 0.9% only.[54] In a study of 148 first infarct NQMI patients, the incidence of in-hospital deaths was 4.1%.[34] The TIMI II Study which included only those patients with ST segment elevation who were then given TPA, the 21-day mortality rate for NQMI was 2.1%.[22] Further subgroup analysis in a study by Nicod et al showed that in-hospital mortality in patients with NQMI was significantly lower than QMI patients only in those older than 70 years.[21]

The reason for the low in-hospital mortality rate in the Groote Schuur Hospital Coronary Care Unit (CCU) may be due to inadvertent patient selection. Firstly, deaths among acute MI patients prior to admission to CCU may have been due to NQMI. Note must be made of the long delay between onset of chest pain and arrival at hospital in those who survived: 7.1 ± 8.8 hours. (The time period for those who died prior to admission to CCU is not known.) Secondly, due to the low capacity of the CCU, many patients with IHD including acute MI are managed in the general medical wards and selection criteria need to be applied when patients in the Emergency Unit are referred for admission to the CCU. Those patients managed elsewhere are not included in this study. These, however, are usually patients who are very stable with minor ECG changes only and who, should they become unstable, are usually re-referred to the CCU. Inevitably, there are those patients who due to multiple medical problems, are not considered candidates for intensive care and therefore are managed in the medical wards. Amongst acute MI patients in the CCU with previous QMI, there may have been NQMI. However, unless the acute MI was clearly evident to be in a previously non-infarct-related region, these patients were excluded from this study. Thirdly, the low in-hospital mortality rate reflects the management and range of support available in the CCU e.g. emergency angiography, intra-aortic balloon pumping and emergency revascularisation.

Early ischaemia after acute MI has prognostic significance. The Ischaemia Residua Study Group, analysing low risk acute MI patients with an otherwise uncomplicated course, showed that

early recurrent ischaemia (defined as spontaneous, transient ST depression or elevation and/or T inversion) which occurred in 8% of their patients, was the only significant predictor of in-hospital cardiac events (deaths, reinfarctions and urgent revascularisations).[136] The GISSI-2 Trial showed that this was unrelated to gender, age, ECG location, thrombolysis or Q or NQMI.[113][136] In a study of 93 patients with NQMI, Ogawa noted that 12 of 13 patients who died in hospital had ST segment depression on ECG and that at postmortem, circumferential subendocardial lesions with triple vessel disease were found in the majority.[137] Based on data obtained from the Diltiazem Reinfarction Study (DRS), it has been shown that 20% of NQMI patients experience one or more episodes of spontaneous post-infarct angina during the primary hospital admission.[48]

This GSH Study, although it did not specifically identify those with ongoing pain separately, but rather grouped them under the unstable immediate outcome, showed no increase in mortality for this group, nor among an additional 9 patients with post-infarct angina during the primary admission, in whom according to accepted policy, urgent angiography was considered to be indicated.

Early recurrent infarction is an important risk factor for early mortality. Marmor et al found that among patients with NQMI, in-hospital mortality was 23% in those with early reinfarction and 8% for those without recurrence ($p<0.05$).[138] Braunwald states that in-hospital mortality in patients with NQMI is approximately 50-60% that in QMI, unless

early recurrent infarction or infarct extension occurs, in which case mortality is similar.[19]

No patients were identified in the GSH Study as having reinfarction or extension of infarction during their primary admission. These may have been missed. Methods of various in-hospital re-infarct studies frequently define recurrence on a biochemical basis (re-elevation of CPK) following routine daily CPK measurement throughout the admission period.[142][143] This is not the routine at GSH.

b) Post-discharge mortality

The one-year mortality rate for all deaths was 9.6% with a 92% follow-up rate. (The Kaplan-Meir survival curve of all deaths in the first year after NQMI is shown in Figure No. 13.) The cardiac death rate for the same period was 7.8%. Of the 16 deaths that occurred during the first year of follow-up, 13 (81%) were due to cardiac causes and 9 (56%) had occurred by the third month. As was noted earlier, NQMI is associated with lower early and in-hospital mortality rates than QMI, but by one year the mortality rates are similar with possibly a higher rate among NQMI patients after the immediate in-hospital period[21] resulting in a "catching up" with the QMI rates. Thus, the early advantage possessed by NQMI patients is soon lost.

The cardiac mortality rate in the GSH Study is mid-way amongst those reported in various studies. The placebo arm of the beta-blocker Heart Attack Trial (BHAT), giving a natural

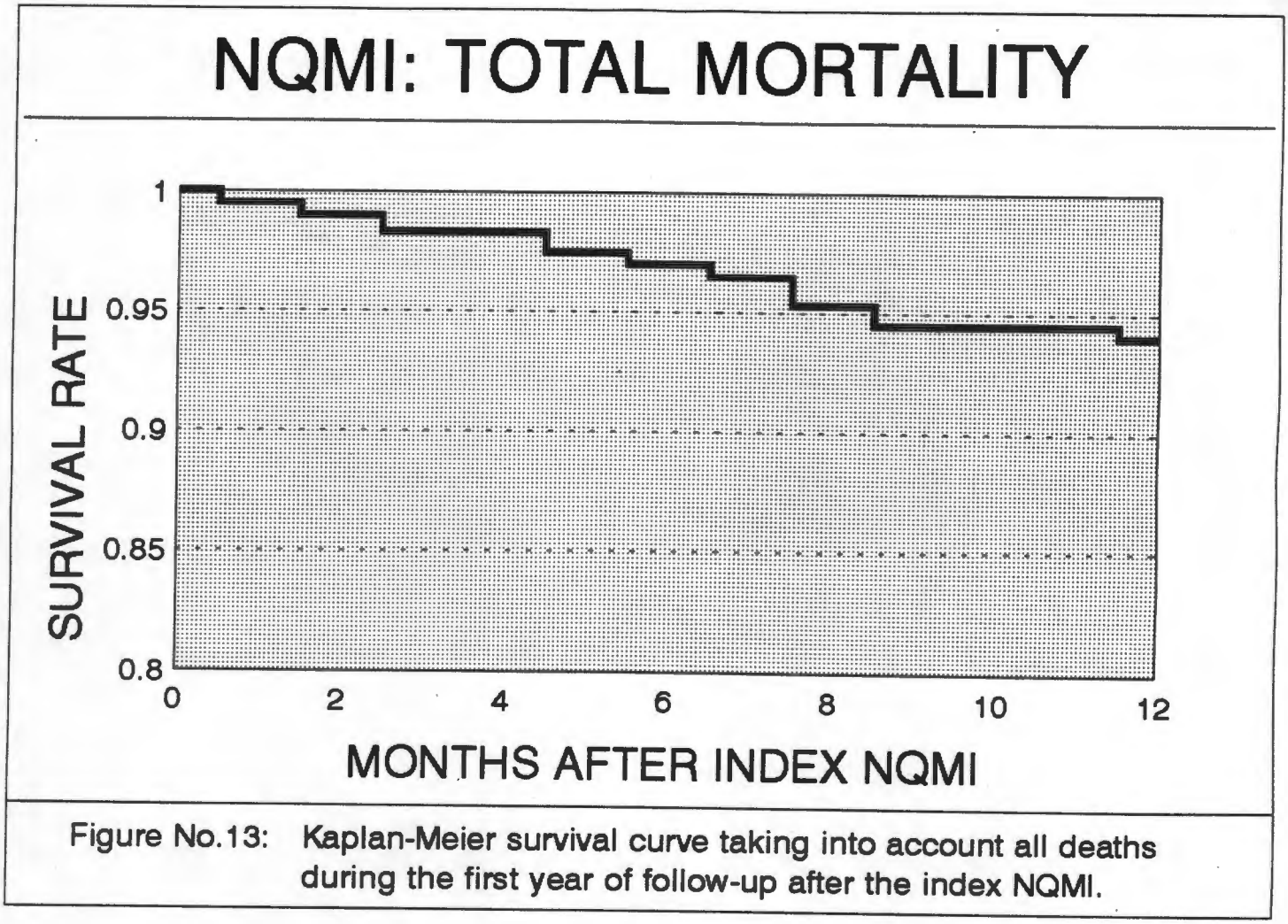


Figure No.13: Kaplan-Meier survival curve taking into account all deaths during the first year of follow-up after the index NQMI.

history in NQMI, showed a one-year mortality of 3.1%.[51] Yet, a 30-month follow-up study on 148 NQMI patients was 16%.[34]

Low rates of mortality (2.4%) among 1473 patients with UAP and NQMI were noted at 6 weeks in the TIMI IIIB Trial.[68] Schechtman et al showed that the mortality rate decreased steadily for the first 3 months and then remained constant.[32] The GSH Study is in keeping with this as shown in the graph relating the number of deaths per month (Figure No. 14).

MONTHLY RATE OF MORTALITY

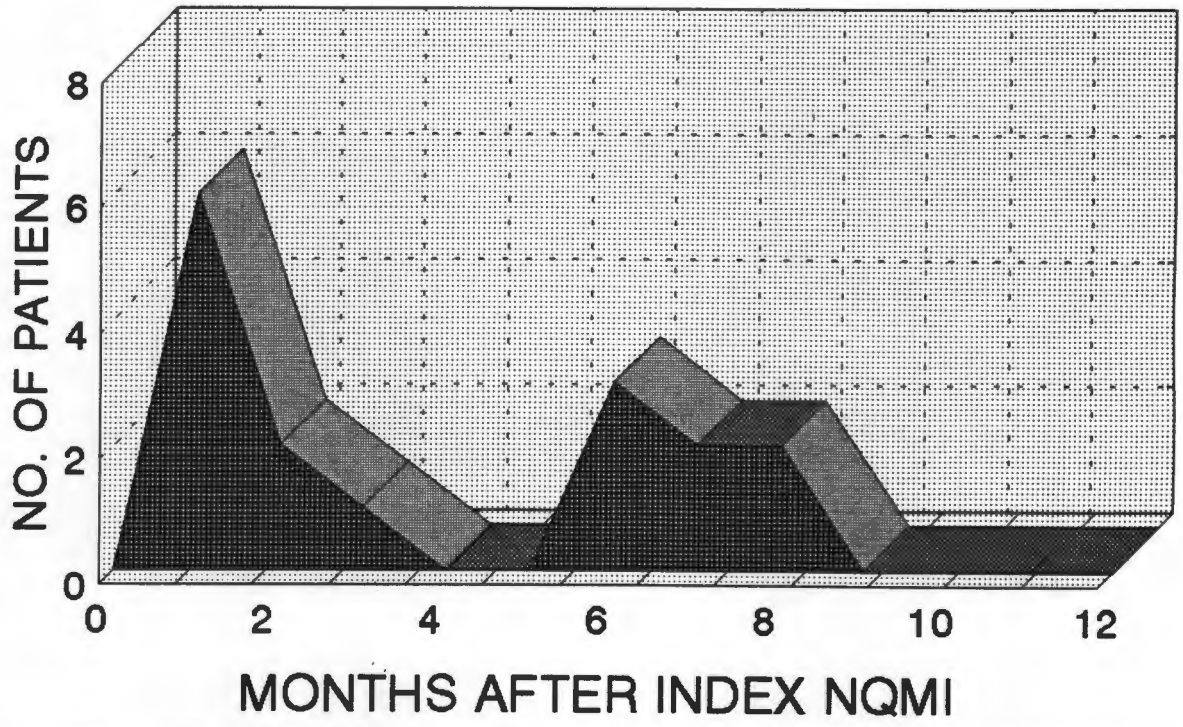


Figure No.14: Monthly rates of deaths after the index NQMI.

On analysis of the GSH data, for identifiable risk factors, univariate methods suggested numerous associations with mortality: age, diabetes, past history of ischaemia, peripheral vascular disease, hypercholesterolaemia, poor early outcome, early cardiac catheterisation, angiographic findings of triple vessel disease and early (<3 month) recurrence of ischaemia. However, only:

- past history of cardiac failure (p=0.002)
- hypotension at primary admission (p=0.01); and
- re-admission for symptomatic recurrence of ischaemia within 3 months of the index NQMI (p=0.004) (Figure No. 15)

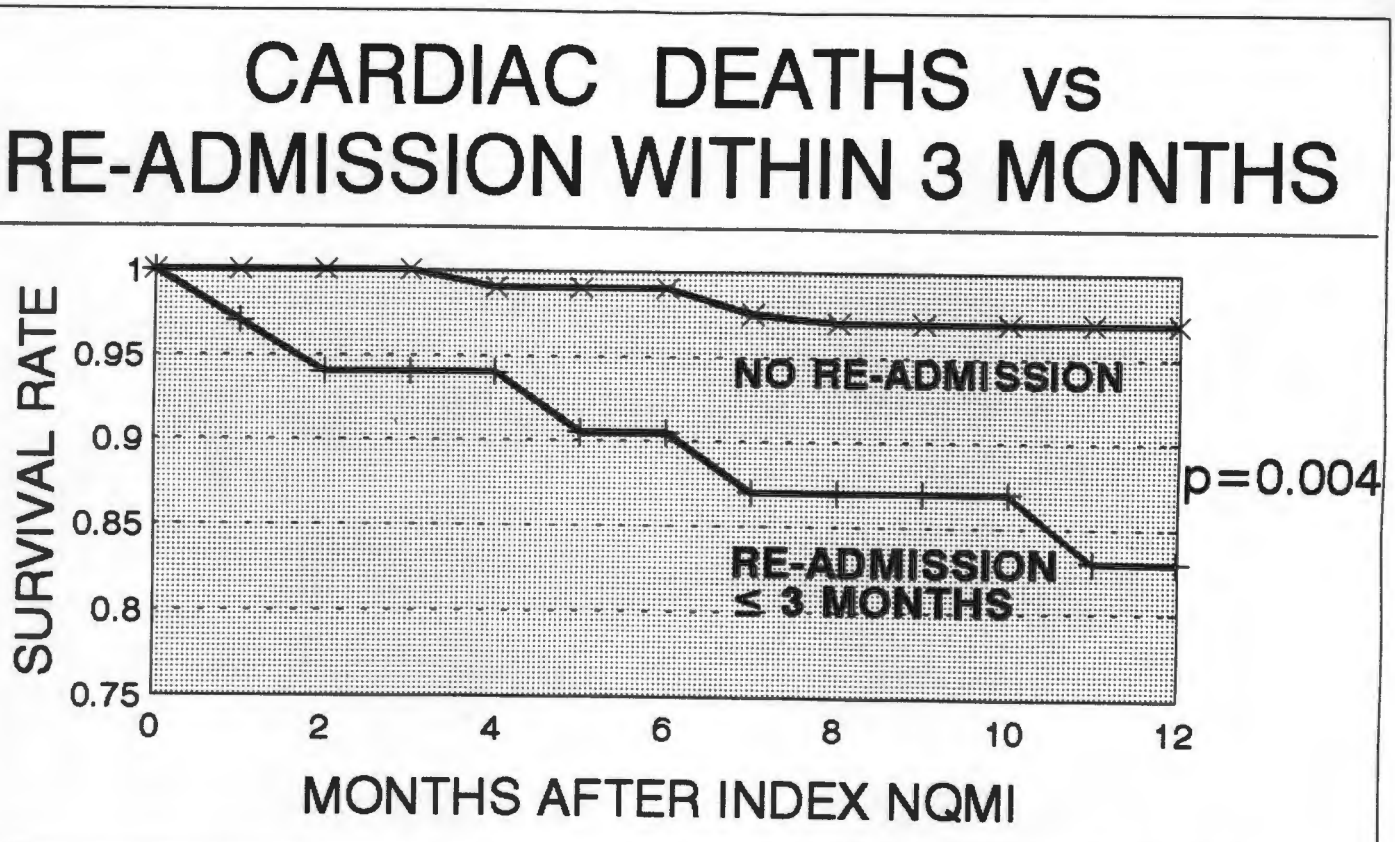


Figure No.15: Kaplan-Meier survival curves of cardiac deaths in the year after NQMI in patients who required re-admission for ischaemia within 3 months and those who did not.

were identified as independent risk factors by multivariate analysis.

Other studies have shown different risk factors for early mortality compared to late mortality.[32] Independent predictors of early mortality noted, include:

- ST segment depression persisting during hospitalisation ($p<0.0001$)
- in-hospital reinfarction ($p=0.0006$)
- history of CCF ($p=0,0255$)

Risk factors for mortality may be apparent very early after admission. Late mortality (at one year) as reported by Boden

from the DRS Study is associated with spontaneous ischaemia after NQMI and before hospital discharge.[96] It appears that even the admission ECG may be predictive of late events. Willich showed that not only does ST segment depression on admission bode poorly, with a higher cumulative one-year mortality, but also severe and multiple lead ST segment elevation is associated with an adverse prognosis.[139]

Independent variables predictive of occurrence of spontaneous pre-discharge ischaemia shown by Pierard et al in a study of 953 patients surviving the first 3 days after acute MI, were:[135]

- history of angina before MI
- NQMI
- absence of smoking
- higher age

These variables: history of past infarction, no smoking and age, statistically could not be shown in the GSH Study to predict for post discharge mortality. Previous studies have shown excess mortality after acute MI in diabetics.[140] The GSH Study showed some univariate association that did not reach significance on multivariate analysis. LVH in patients with NQMI has been associated with higher rates of mortality and reinfarction.[141] This was not examined for in this study. However, most of these variables are not specific for NQMI and are equally valid for QMI.[135][32][61]

The mortality findings and associations need to influence management both during the primary admission and subsequently. The TIMI IIIB Trial showed that a low incidence of 42-day mortality of 2.1% can be achieved in a relatively high risk group (all patients with ST segment depression) by immediate hospitalisation, bedrest and vigorous use of anti-ischaemic treatment, IV heparin and oral aspirin.[68] The TIMI II Trial showed that a low one-year mortality in NQMI patients of 3.4% can be achieved following administration of TPA to patients with ST segment elevation.[22]

The GSH Study suggests that patients with previous cardiac failure and who were hypotensive on admission need to be watched carefully. watched carefully. Since admission f of ischaemia within 3 months was a significant risk factor - this itself must be addressed. Obviously ST segment depression pre-discharge, reflects more than just mechanical damage, but is an indication of ischaemia requiring active management. Prophylaxis against recurrence of ischaemia is therefore strongly indicated.

3) **Recurrence of Ischaemia**

Recurrence of ischaemia is important, not only because of considerable morbidity, but also because of, as seen previously, the strong association with post-infarct mortality[91] which applies even to that group of low risk patients with an otherwise uncomplicated course as shown by the Ischaemia Residua Study Group.[136]

In the GSH Study, recurrence refers to the earliest symptomatic recurrence of myocardial ischaemia after discharge from CCU, which may have required re-admission, or not. As noted in Study Methods, patients with acute MI at GSH do not routinely undergo tests to provoke ischaemia e.g. exercise stress test, radionuclide stress testing or tests of silent ischaemia e.g. Holter ECG monitoring. Rather, recurrence of ischaemia is awaited by the spontaneous declaration of further symptoms. Since patients were included into this study by retrospective analysis of ECGs (looking specifically for non-QMI) and admission findings, patients with ECGs that showed late development of Q waves not associated with recurrence of chest pain were excluded. NQMI extensions or in-hospital reinfarctions (by CPK iso-enzyme criteria) were not considered as separate events unless accompanied by chest pain and ECG changes. Definitions of extension vary and may include ECG and enzyme re-elevation above the preceding baseline only.[142][143] In addition, studies have shown that in 20% of patients with NQMI who have infarct extension, new Q waves develop when these were initially absent.[143][144] If these developed during the primary admission, the patients would have been excluded from the GSH study. Furthermore, prior to discharge from the hospital, patients are mobilised in the general medical wards. Early recurrence of ischaemia may have occurred and may have remained unreported. Thus, the true frequency of both reinfarction and recurrence of ischaemia may be underestimated. Despite possible underestimation, a very high early recurrence rate was noted. (Early recurrence was defined as occurring within 3 months.) (Figure No. 16)

NQMI: MONTHLY RATE OF FIRST SYMPTOMATIC RECURRENCE OF ISCHAEMIA

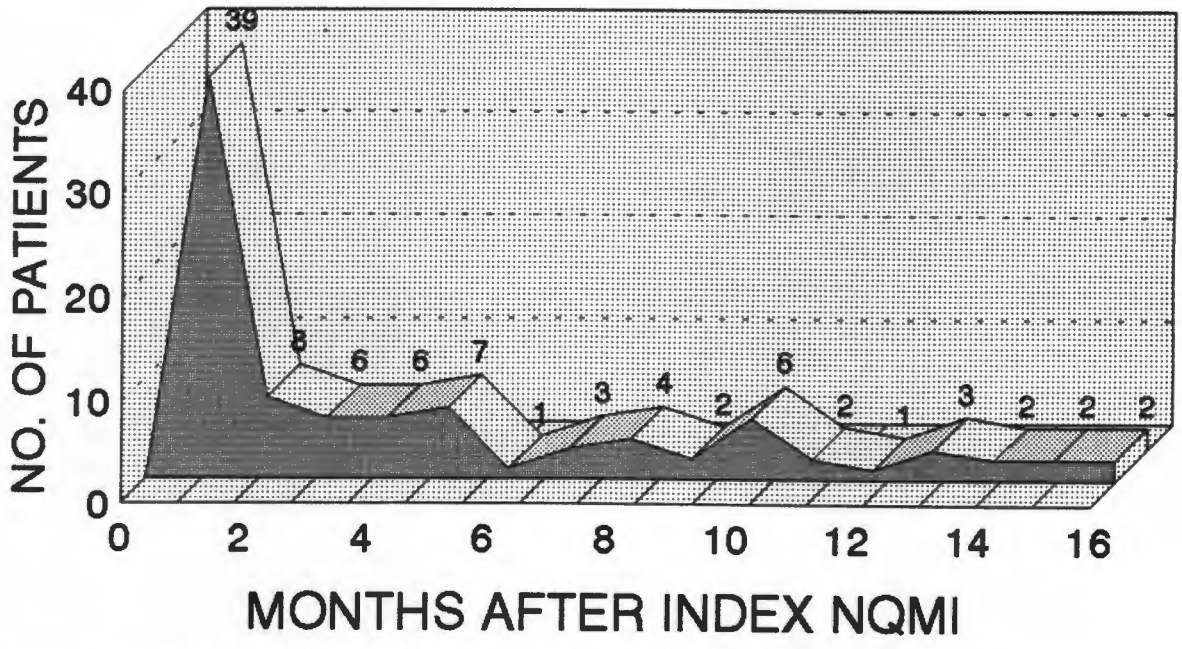


Figure No.16: Monthly rate of the first symptomatic recurrence of ischaemia after the index NQMI.

By one year (with a follow-up of 92%), there was a recurrence of symptomatic ischaemia in 51.2% of patients. Of this group:

- 46% had occurred within the first month,
- 62% within the first 3 months and almost two thirds required re-admission.

The monthly rate of recurrence, as shown in Figure No. 16, is particularly high in the first 2 months, falling off rapidly and remaining constant thereafter. Due to possible under-estimation, the recurrence rate within the first month may actually have been higher. As these rates refer only to spontaneous symptomatic ischaemia, active search for inducible ischaemia (e.g. EST, radionuclide stress test or silent

ischaemia), which usually is performed within one month to six weeks after discharge, may have elevated these early figures even more.

The strikingly high recurrence rate coincides with the findings of other studies. A meta-analysis by Nixon showed a recurrent angina rate of 47% post NQMI.[24] If one extrapolated to include NQMI under the old classification of subendocardial MI, a study by Madigan et al found that unstable angina occurred in almost half the patients with NQMI during a follow-up period averaging 11 months.[145]

Analysis of the GSH data to establish risk factors has been divided into:

a) those predicting for recurrence of symptoms by three months, and
b) those predicting for recurrence by 12 months.

a) Early symptomatic recurrence is statistically significantly and positively associated with numerous variables:

- pre-infarct: hypertension and hypercholesterolaemia
- peri-infarct: NQMI not localised in the inferior territory and interestingly lower CPK elevation and use of thrombolytics
- post-infarct: no early catheterisation (i.e. conservative management and particularly no early revascularisation); also non-use of aspirin.

However, with multivariate analysis, only early revascularisation remained a significant, but negative risk factor. It is interesting that lower CPK values and thrombolysis showed a trend to increased risk. One may speculate that this reflects smaller area of infarction and therefore more jeopardised or viable myocardium at risk.

b) Analysis for symptomatic recurrence of ischaemia by 12 months again links thrombolysis, no early catheterisation and no early revascularisation with a higher recurrence rate. No smoking is also associated with a higher recurrence. Multivariate analysis singles out early revascularisation plus inferior territory infarcts as being significant independent negative risk factors.

The mechanism of recurrence of ischaemia following thrombolysis can be readily explained. Viable, salvaged myocardium persists distal to the un- or partly resolved arterial stenotic lesion and is thus at risk of further recurrent episodes of ischaemia. However, why this subset of aborted QMI should be at a significantly higher risk than the rest of the NQMI group of patients ($p=0.015$) where the same mechanism exists, is not clear. It is noted statistically that significantly fewer thrombolysed patients underwent early catheterisation as compared to those who did not receive thrombolytic agents ($p=0.005$).

That inferior infarction is associated with a lower risk is not surprising[146][63][147] and will be discussed more fully under NQMI Location.

The GSH data show that 12-month survival after NQMI without significant morbidity, is 46%.

Commentators on other studies which have also shown that most recurrence occurs early, indicate that the main effort of physicians should not be spent on management of the acute event, but rather on the prevention of recurrence of myocardial ischaemia and infarction.[33] The retrospective analysis of the GSH data appears to be in keeping with this and suggests that early investigation by catheterisation for the purpose of early revascularisation reduces the risk of subsequent recurrence.

4) **Reinfarction**

Reinfarction is important because it not only re-exposes the patient to peri-infarct-related acute complications, but is, as has been discussed, associated with higher death rates and among those who survive further deterioration in ventricular function.[143]

In this GSH Study, the reinfarction rates were 2.9% and 9% at 3 months and 12 months respectively. As usual, other studies give a wide scatter of rates from 4.7% at one year in the placebo arm of the BHA Trial (essentially a natural history study of NQMI)[51] to 21% of NQMI, then called subendocardial MI in a study by Madigan.[145]

There is greater discrepancy among studies with regard to early reinfarction rates. In the TIMI IIIB Trial, reinfarction by 6 weeks had occurred in 6.3%.[68]

Reinfarction rate at 2 weeks in the Diltiazem Reinfarction Study was 9.3%.[142] Yet, a prospective study of "subendocardial infarcts" by Marmor et al, showed that 43% had recurrent myocardial infarction within 10 ± 4 days after the initial episode and that this group's mortality rate doubled.[143] The high figure relates to their definition of recurrent infarction as being a secondary rise in plasma CPK-MB levels. This criterion was not used in GSH; therefore, if the second MI was silent or if it resulted in Q waves, these patients may have been excluded.

Numbers in the GSH Study are small. Risk factors for reinfarction by univariate analysis appear to be recurrence of symptomatic ischaemia and re-admission by 3 months. Re-infarction is less frequent in those patients with inferior MI and in those who had early investigation. Age and past history variables were of no significance.

Risk factors for reinfarction in other studies are: spontaneous post-infarction angina[103] as shown in the DRS Study and baseline hypertension (in the Framingham Heart Study).[10] Associations have been noted with a history of previous MI, angina, congestive heart failure and diabetes and with triple vessel disease on coronary angiography in a study by Gilpin in a large population of 3666 acute MI patients.[61] Angina pectoris, however, was the single most important factor related to reinfarction on multivariate analysis. This supports the practice of performing coronary angiography in patients with angina pectoris on follow-up after NQMI.

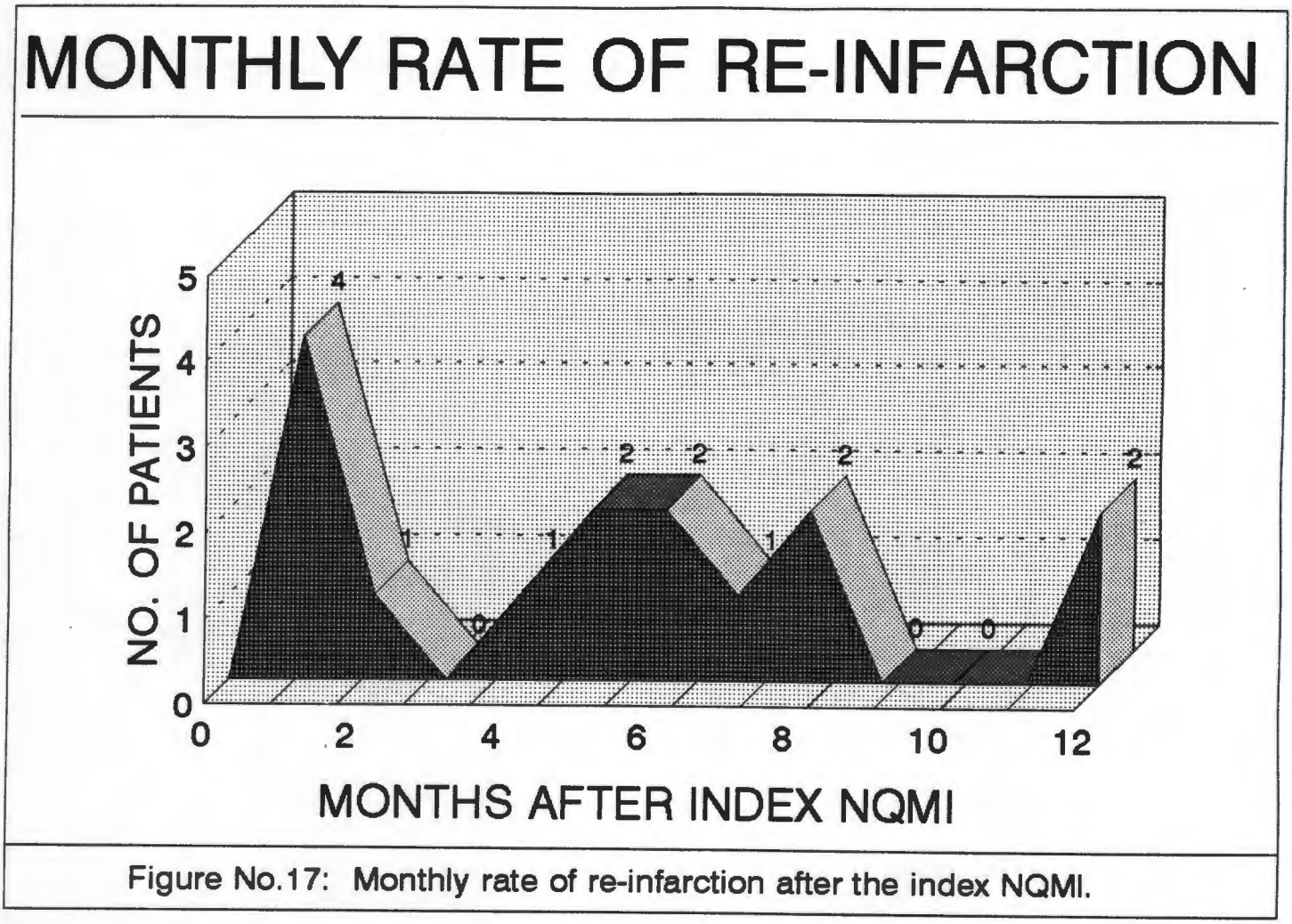


Figure No.17: Monthly rate of re-infarction after the index NQMI.

Studies have also suggested that early reinfarction involves the same coronary artery and site of obstruction, as during the index NQMI in up to 90% of cases.[97][143] After about 6 months, infarction occurs in the same area in only 50% of cases and in 50% randomly. Such analysis is not possible in the GSH study where infarct recurrence was not assessed by routine follow-up ECG, but refers either to symptomatic infarcts requiring admission or to infarcts reported in patients re-admitted to the medical wards, not specifically for MI, but for UAP or cardiac failure.

5) **Early Conservative Versus Early Active Management**

All the patients in this study were retrospectively divided into two groups: (The decision on management had been taken

by the physician caring for the patient on a variety of clinical indications)

a) Early active management:

This refers to management of NQMI patients during the primary admission by means of cardiac catheterisation and angiography with the prime objective of performing a revascularisation procedure (either coronary artery bypass grafting [CABG] or percutaneous transluminal coronary angioplasty [PTCA]) if coronary anatomy was suitable.

b) Early conservative management:

This group consisted of those NQMI patients who did not have cardiac catheterisation during the primary admission to CCU. Their subsequent management was expectant and included cardiac catheterisation (again with view to revascularisation) if indicated by e.g. recurrence of ischaemia. Active search for inducible ischaemia by means of exercise or radionuclide stress testing post-acute myocardial infarction, was not the general policy of the GSH Cardiac Clinic as it was felt that recurrence of ischaemia would declare itself spontaneously, usually on mobilisation either in CCU or after transfer to the general medical ward before discharge from hospital. In either group, for the purpose of analysis of outcome of the management strategies, recurrence of symptomatic myocardial ischaemia (including re-admission with angina and/or reinfarction and cardiac deaths) was considered to be a failure.

(As stated in Study Methods, all patients admitted to the CCU received intravenous heparin, aspirin orally and Beta-blocker, unless contra-indicated or not tolerated.)

Analysis of the study data reveals that 93 patients underwent cardiac catheterisation during the primary admission to CCU. (Follow-up data is available for 92 of the patients.) The indications, which have been listed, included all the well-accepted ones: recurrence or ongoing chest pain and also, some patients purely for the reason that they were NQMI. Although it was difficult at times to determine retrospectively what the consultant cardiologist's primary intentions were, at least 24 patients had cardiac catheterisation for no reason other than they had had a NQMI. A further 19 were actively managed because they had NQMI, plus an ECG that "looked ischaemic" with either ST segment depression or T inversion.

In the group managed with active intervention, 50 patients were recommended to undergo a revascularisation procedure (13 PTCA and 37 CABG). Furthermore, in 12 of the 43 patients who were advised to have medical treatment primarily, revascularisation was considered to be an alternative action if symptoms recurred. Thus, medical treatment as the only option was the outcome of active investigation in 33.3% of the patients.

The conservatively managed group consisted of 88 patients, although follow-up data is only available on 82. In this group, none of the indications for cardiac catheterisation

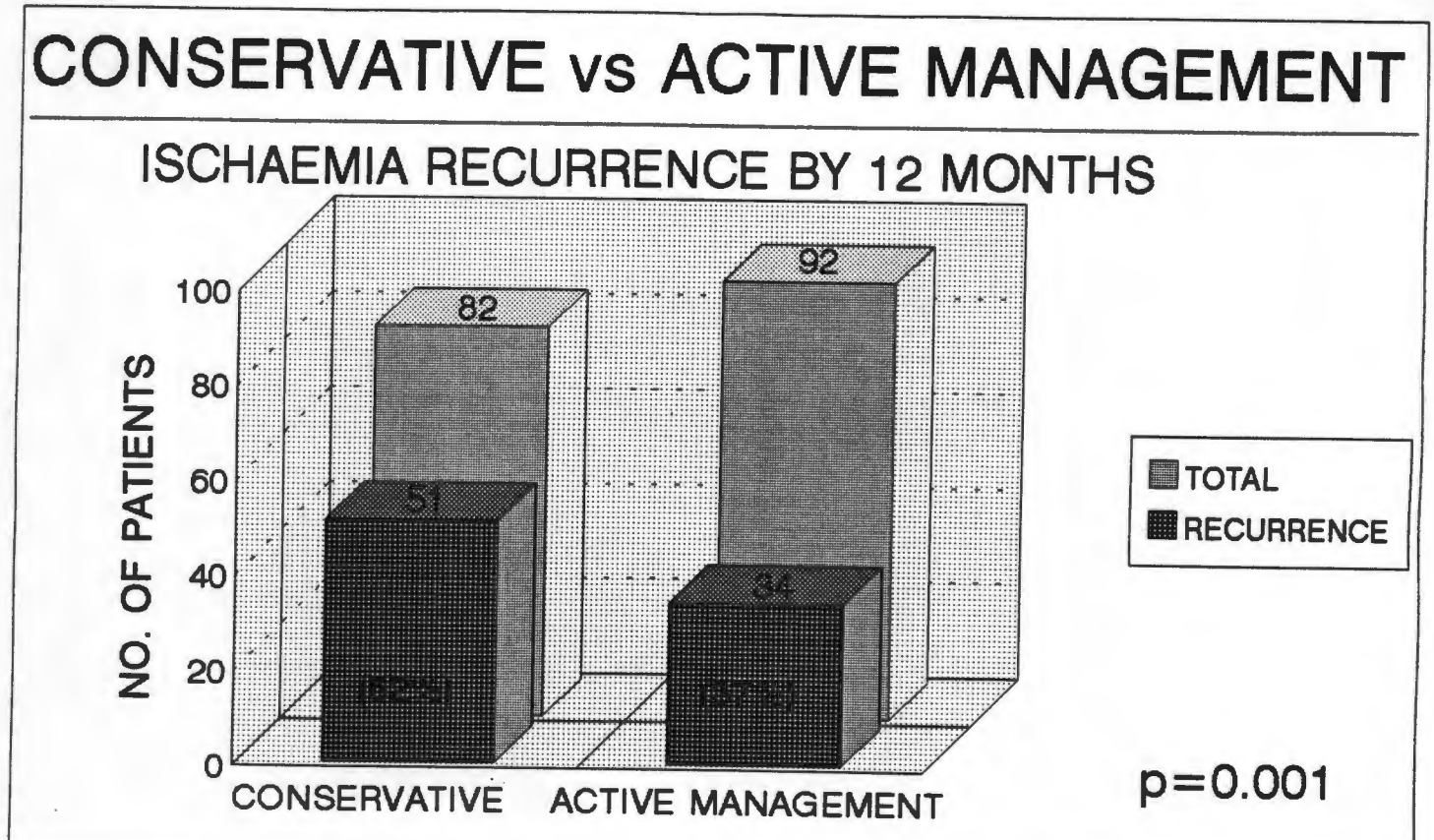


Figure No.18: Recurrence of symptomatic ischaemia in the first year after NQMI in patients who were managed conservatively versus actively investigated during the primary admission.

listed previously were present. Thus, in essence, this group was considered at low risk i.e. low risk of complications including recurrence of ischaemia.

No statistically significant differences were noted in the demographic characteristics of the patients of both groups nor in the NQMI location.

Analysis of these two retrospectively divided groups is summarised in Figure No. 18. Of the 82 patients who were initially treated conservatively, there were 51 who had recurrence of symptomatic ischaemia within 12 months. In the actively managed group of 92, only 34 had similar recurrence. Statistical significance was p=0.0009. Active management was

associated with a 25% risk reduction of recurrent ischaemia. The difference at 3 months was just within acceptable limits of significance (p=0.047). Analysis also revealed significantly lower re-admission and reinfarction rates, both at 3 and 12 months in the actively managed group. However, no statistically significant difference was noted with regard to mortality.

The results may, therefore, appear to justify active intervention. However, it must be remembered that this was not a natural history study or a randomised prospective trial, but a non-randomised retrospective analysis. Risk stratification had inevitably taken place in the recommendation of active intervention/investigation.

Bearing in mind the limitation of this study, it is worth noting that the conservatively managed group, despite being obviously low risk (otherwise the patients would have been catheterised) still had a higher recurrence rate than the early actively managed patients.

The fact that no favourable effect on mortality was noted, is reminiscent of numerous other studies relating to cardiac disorders where significant improvement in symptoms has been noted, but no long-term survival benefit has been achieved.

(The GSH experience appears to parallel that of a group in Israel who recently reported a retrospective study with an improved outcome in patients with a first anterior NQMI treated with an early invasive approach.[148])

6) **Early Conservative Versus Early Active Management in NQMI Alone**

As mentioned in the previous section, 24 patients underwent early cardiac catheterisation purely for the reason that they had NQMI (to be called Group A). They were in all other respects, low risk and therefore equivalent to the group that was initially managed conservatively (Group B). In fact, Group A was a little different to the remainder of the early actively managed patients who were all clearly higher risk patients in whom there was also a trend to more revascularisation - 41 of 68 patients (as opposed to 9 of 24 in Group A) ($p=0.05$). During the follow-up period, 16 patients in Group B underwent cardiac catheterisation for recurrence of ischaemia.

Thus, Group A and B represent what would have been the ideal if this study were randomised and prospective - all essentially low risk, with one group undergoing active intervention.

This, however, is a retrospective study. Taking cognisance that such subanalysis tends to lose statistical significance, particularly with the low population numbers, and may also be considered 'dangerous' if routine practice and management should be significantly changed as a result of possibly suspect analysis, it is still interesting to speculate what the results of a study such as this would be - this if only to guide proposals for a future prospective randomised study.

Comparisons of the demographics, use of thrombolytics, previous MI, NQMI localisation and CPK levels revealed no statistically significant differences except for age with Group A having a mean age of 48.5 years and Group B, 57.3 years ($p<0.001$).

Analysis of differences in recurrence of cardiac events in these two groups showed no significance for recurrence of symptomatic ischaemia nor for cardiac deaths. Significant differences in re-admission and reinfarction were noted between Group A and B, but only at 12 months after the index NQMI with lower rates in Group A (Figure No. 19). (There were no significant differences in any of these respects between Group A and the rest of the early catheterised group).

One may conjecture as to the meaning of such results. Firstly, the fact that there appeared to be no significant difference in symptomatic ischaemia indicates, provided it was not due to lack of numbers, how equivalent the two groups were regarding risk. Secondly, the statistical difference with lower rates of reinfarction and re-admission in Group A shows either that active investigation, even in a low risk group such as represented by Group A, has benefit or reflects the only other significant difference as mentioned before - the younger age in this group. However, why does this not affect cardiac mortality? Interpretation here becomes exceedingly tenuous as the numbers are small.

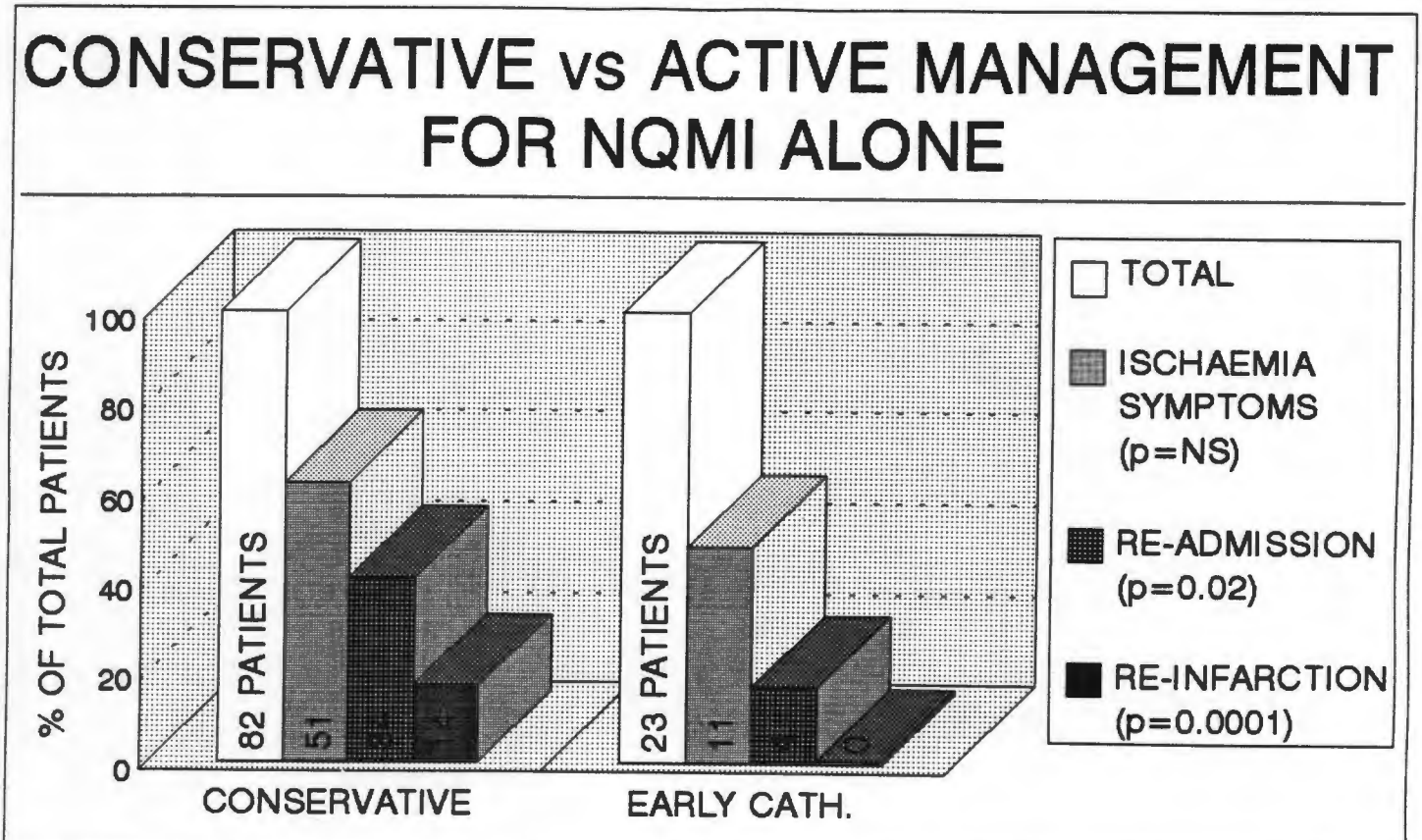


Figure No.19: Comparison of recurrence of symptomatic ischaemia, recurrence requiring re-admission and reinfarction by 12 months in patients managed conservatively (NQMI with no other indication for early catheterisation) vs patients who were catheterised early where the only indication was the index NQMI.

The difficulty with interpretation of these results and those in the previous section is the lack of active search in the conservative group of inducible recurrence of ischaemia. Pre-discharge exercise stress testing (and radionuclide stress testing) as discussed previously, is effective in NQMI, both in provoking ischaemia and marking individuals at higher risk of subsequent complications and risk stratifying a group with low risk. Only 9 patients underwent exercise stress testing in the GSH Study.

Other studies have also tried to evaluate conservative and active strategies. In the NQMI subanalysis of the TIMI II Study (patients with acute MI who presented with ST segment elevation and were given TPA), in the conservatively managed

group (which did include EST in all patients) cardiac catheterisation (equivalent to treatment failure) was performed by day 42 after thrombolytic therapy in 47.5% and subsequent revascularisation in 27.6% of the patients.[22] The outcomes of conservative management and the invasive strategy showed no significant differences in death, fatal or non-fatal reinfarction 42 days after lytic therapy. Reported reasons for performing the catheterisation before hospital discharge in the conservative group were:

- recurrent ischaemic pain 46.2%
- suspected reinfarction 5.6%
- abnormal EST 2.1%

The data would suggest that pre-discharge EST has little value. However, the published results do not tally as 71% (928) of all the analysed conservatively-managed infarct patients completed a hospital discharge exercise test. Thirty-three percent had a positive or equivocal result and 32% went on to catheterisation. No data is available for the period between discharge and day 42.

The TIMI IIIB Study evaluating conservative and active management in patients who presented with ST segment depression, also showed equally satisfactory clinical outcomes whether managed by either invasive or conservative strategies.[68] In this study, by day 42 after initial randomisation, 64% of the early conservative group had had catheterisation (with 90% occurring before discharge) and 49% had revascularisation. The mean time to catheterisation was

7.1 days. Review of the study publication does not reveal the number of patients in the conservative arm that underwent catheterisation for recurrence of symptoms or positive EST.

Are these studies comparable to the GSH Study? There are three major differences:

1. The conservative group in the retrospective GSH Study was a selected low risk group i.e. the remainder in whom no indication could be found for catheterisation during the primary admission. In both TIMI II and TIMI IIIB, the conservative groups were randomised on admission and were clearly not low risk, as noted by the mean time to catheterisation of 7.1 days in the TIMI IIIB Study. Yet, the GSH Study appeared to relate an unfavourable outcome to the otherwise low risk group.

2. The GSH Study groups were highly heterogeneous including the whole spectrum of NQMI. These two TIMI studies had highly selected homogeneous groups of patients, with regard to ECG, yet were not purely NQMI, the diagnosis of which was made post-randomisation. Hence, these TIMI studies do not encompass the entire gamut of NQMI.

3. Both TIMI studies performed pre-discharge EST in their conservatively managed patients, unless they had already reached the endpoint of a recurrent cardiac event. (However, it is not clear to what degree this altered management.) EST results from other studies show a considerable number to be positive. In a study of the

clinical and functional distinctions between Q and NQMI, Gibson reported that 55% of the NQMI patients had either angina or ST segment depression during the pre-discharge EST with 20% experiencing limiting angina resulting in test termination[55]. If this policy of a pre-discharge EST had been applied to the conservative strategy group in the GSH Study, it is possible that the majority of this already low risk group that subsequently had further complications, could have been identified. The result may then have shown that early conservative strategy (which in fact, was not as "early" as in either of the TIMI trials) was at least equivalent to early active intervention. After all in the GSH study, 48.8% of the total group of 181 NQMI patients and 37.8% of the conservatively treated group of patients, did not have any recurrence in the first year after the index NQMI. If one performs good evidence based risk stratification, it is possible that the resulting group assessed as being of low risk, will coincide with these groups without any recurrence.

1B. GENERAL RESULTS

1) Demographic Characteristics: Age and Gender

a) Age

Since progressive coronary artery disease is associated with advancing years, the ages of patients included in any study within the spectrum of ischaemic heart disease, may play a major role in influencing the outcome.

This has been seen in numerous studies. In a large patient study (n=2024) assessing the clinical outcome after Q and NQMI

AGE OF NQMI PATIENTS

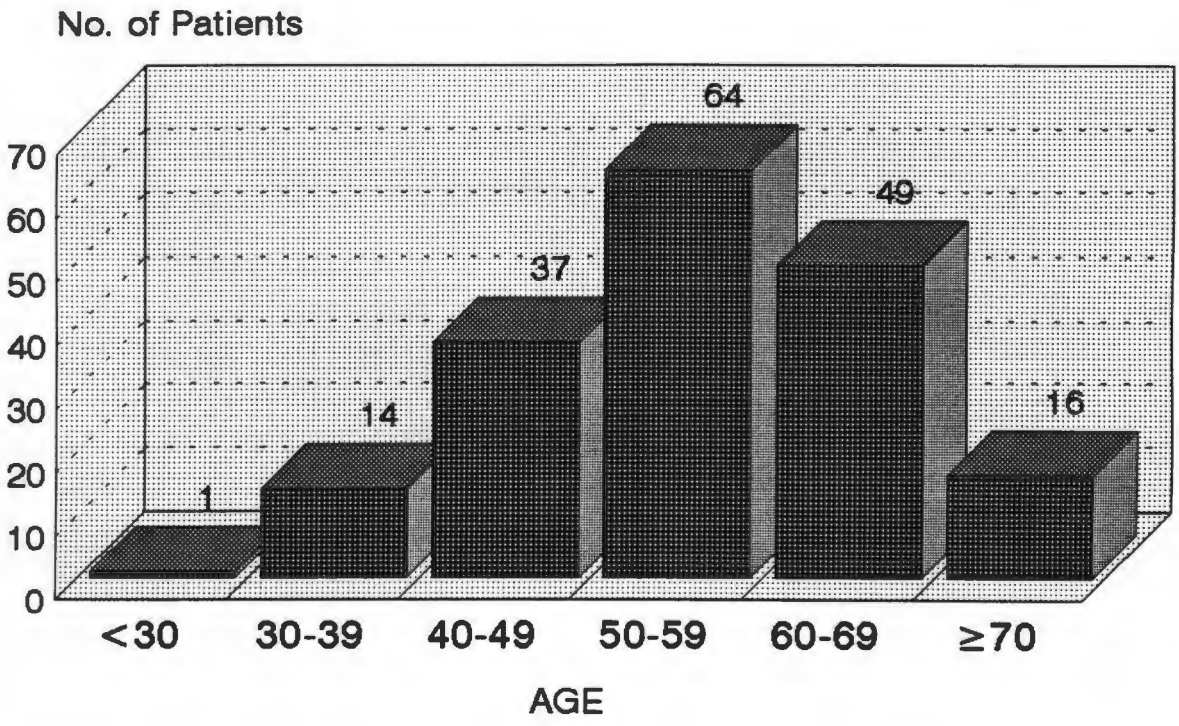


Figure No.20a: The age frequency of patients admitted with NQMI 1990-1993.

EARLY CATHETERISATION, EARLY REVASCULARISATION & SMOKING vs AGE

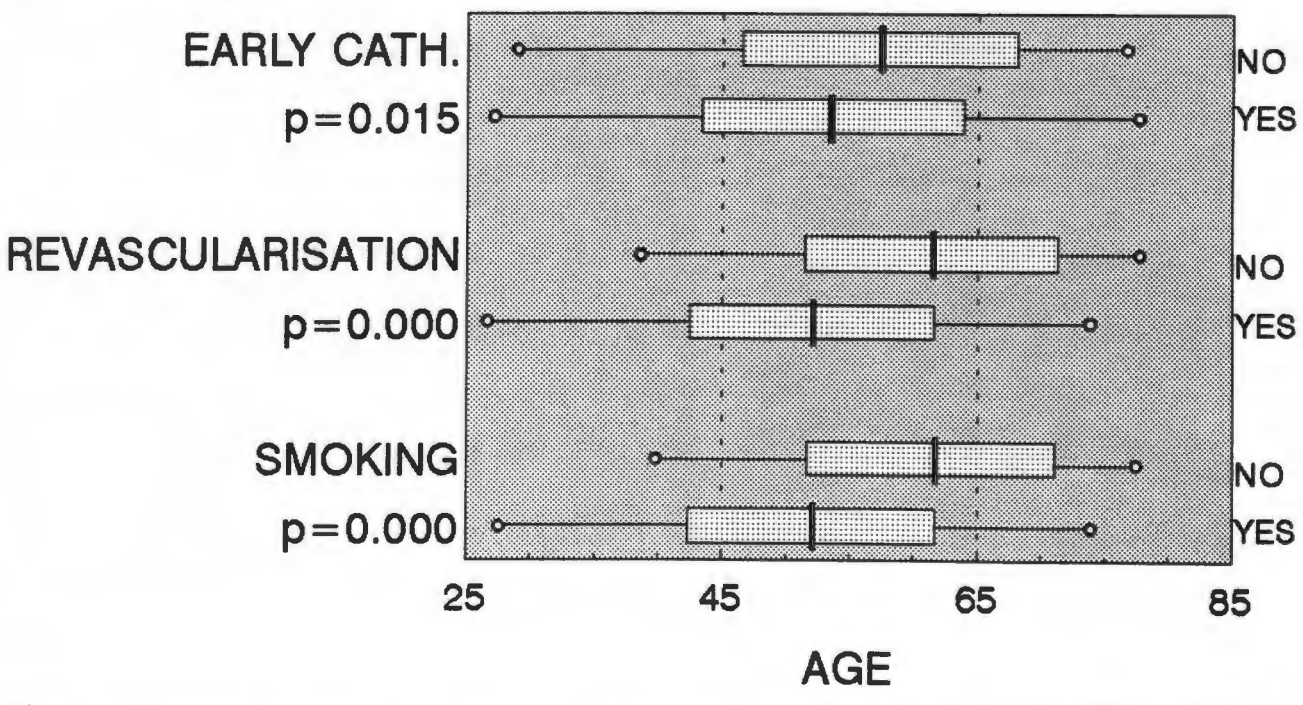


Figure No.20b: Multiple boxplots giving mean, standard deviation and range with statistical significance in the comparison of those who had early catheterisation, early revascularisation and smoked versus those who did not.

where the mean age of the patients with NQMI was 65 years, the in-hospital mortality for NQMI was shown to be significantly lower than QMI, only in patients older than 70 years. On the other hand, patients ≤70 years with NQMI do not have increased risk of death at one year compared to those with QMI.[21]

In-hospital mortality may not differ much between older and younger NQMI patients; one-year mortality, however, is significantly higher in the elderly.[26] Not only is long-term prognosis poorer, but NQMI patients >70 years are more likely to develop atrial fibrillation and cardiac failure, and less likely to receive thrombolytic therapy, cardiac catheterisation and coronary angiography.[26]

The higher mortality rate in these patients suggests that this subgroup of NQMI may benefit from more aggressive treatment. Data from the TIMI IIIB Trial supports this contention as patients >65 years presenting with UAP or NQMI appeared to derive significant benefit from early catheterisation and revascularisation if anatomically feasible.[68]

In the GSH Study, the mean age of 55.3 ± 10.7 years, appears to be younger than other studies.[21][68][22] Although age was statistically associated with poorer immediate outcome following NQMI and mortality (particularly overall total mortality), in multivariate analysis, age was not found to be a significant or independent risk factor for either outcome or cardiac deaths by 12 months. Interestingly, age was not related to the recurrence of post NQMI symptomatic ischaemia. There was a significantly lower early catheterisation rate in

patients ≥70 years (p=0.001), however, no differences in revascularisation rates among those catheterised, were noted.

b) Gender

Myocardial infarction in women has a similar clinical presentation as in men with the exception of increased incidence of NQMI. Differences between the genders in the period after any type of infarct become more evident, particularly with regard to mortality.

Analysis of causes of higher in-hospital mortality in women after acute MI has shown that women are older, have more systemic hypertension, higher cholesterol levels and seek medical care later. Yet, coronary angiography has shown similar vessel involvement and severity of coronary artery disease.[149] A study analysing this showed that 5 variables predicted for higher in-hospital mortality in women: age >65 years, diabetes mellitus, shock, NQMI and not undergoing cardiac catheterisation. It concluded that the difference in hospital mortality between men and women is due to a combination of pre- and in-hospital factors in women and not due to differences in disease severity.[149]

With regard to morbidity, Marmor et al implicated obesity and female gender as predisposing factors for reinfarction in post NQMI patients.[138]

In this GSH study, females formed about one-third of the total number of NQMI patients (Figure No. 21). Although the average age of females was higher (57.3 ± 9.7 years) as compared to

GENDER IN NQMI PATIENTS

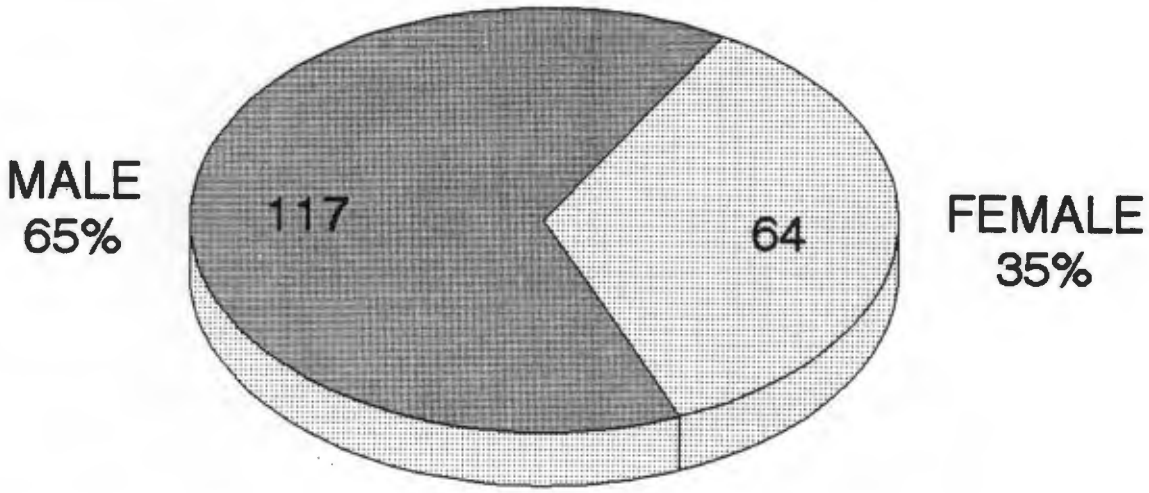


Figure No.21a: Analysis of NQMI patients 1990-1993 by gender.

SMOKING, REVASCULARISATION vs GENDER

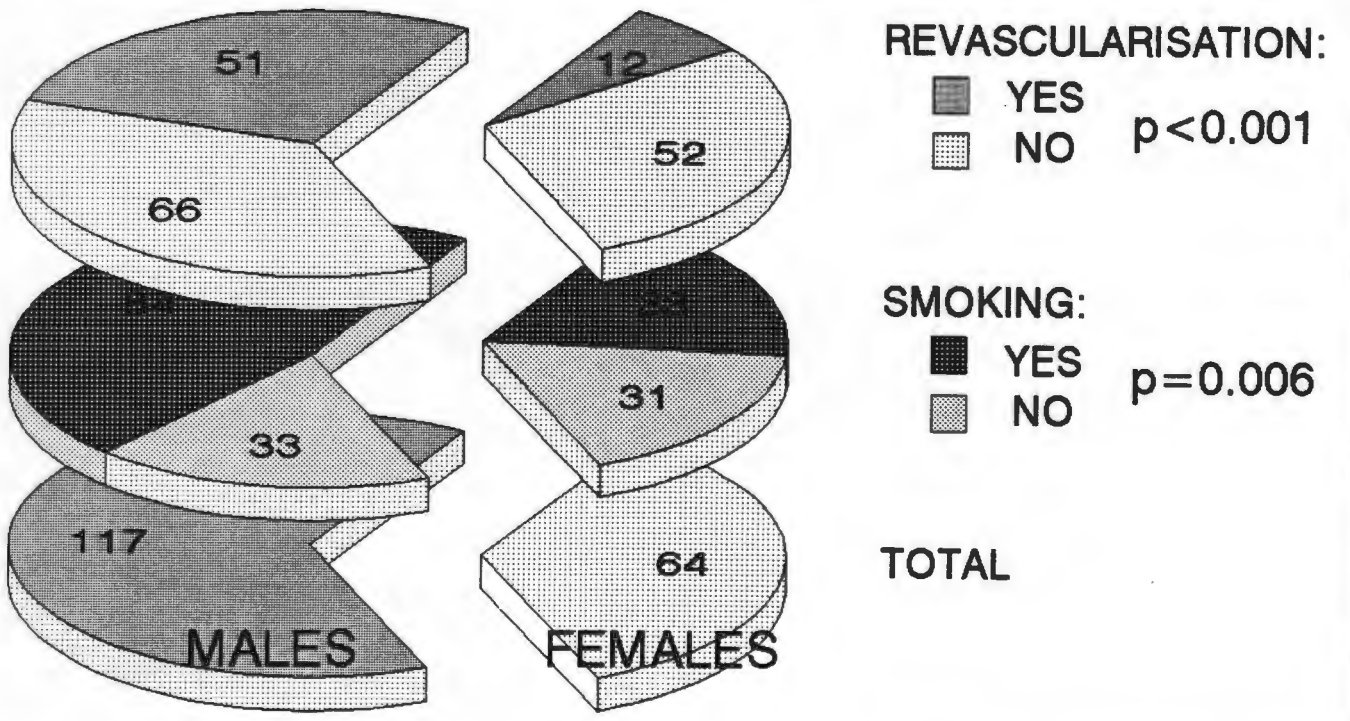


Figure No.21b: Comparison of the proportion of males and females presenting with with NQMI who smoked and who underwent revascularisation and the levels of statistical significance.

males (54.2 ± 11.1 years), this was not statistically significant.

Revascularisation as noted in other studies was also gender-dependent. In total, 12 women (18.8%) versus 51 men (43.6%) underwent PTCA or CABG ($p<0.001$).

2) **Habits: Smoking and Alcohol Intake**

a) In this study, smokers were shown to be statistically related to immediate outcome and recurrence of ischaemia, although they were not shown to be independent variables on multi-variate analysis. Remarkably, this was an inverse or negative relationship, i.e. smoking was associated with a lower incidence of immediate instability or recurrence of ischaemia. Such a relationship has been shown in studies with smokers having an improved survival after MI compared to non-smokers.[150][134] Reasons for this were studied in 2955 patients with acute MI, by Kelly et al, who found that both early (1 month) ($p<0.0001$) and late (12 months) ($p<0.01$) mortality rates were lower in the smoking population. The fact that smokers as compared to non-smokers were 10 years younger ($p<0.001$), had lower prevalence of hypertension ($p<0.01$), CCF ($p<0.00001$), angina pectoris ($p<0.01$) and diabetes mellitus ($p<0.0001$), appeared to explain this. When adjusted for age and the other variables, they eliminated the differences in late mortality rates, suggesting that not smoking at the time of acute MI does not appear to be an independent predictor of death during the first year after acute MI.[134]

In the GSH Study, the mean age of non-smokers was 61.4 ± 2.4 years and of smokers 52.0 ± 1.8 years ($p<0.0001$). Differences may, however, not only be attributable to the younger age of smokers. Smokers have been shown to differ in their site of infarction compared to non-smokers.[149] In addition, it is possible that smokers may have more sudden death or pre-hospital admission deaths related to their acute MI and thus, only the survivors have selected themselves out.

The GSH Study data reflects the use of tobacco in the South African society, not only with 65% of the total patients, but also in the breakdown by gender, with 52% of the females and 72% of the males ($p=0.007$) admitted with NQMI, being smokers.

b) In a similar way to smoking, alcohol use was related to a better immediate outcome although by multivariate analysis it did not independently predict for this. Alcohol has cardioprotective effects and may beneficially alter serum lipoprotein concentrations and promote coronary-artery vasodilatation. This may account for the approximately 30% reduction in the relative risk of fatal and non-fatal coronary heart disease among moderate drinkers as compared with non-drinkers, as shown in other studies.[151] However, this GSH Study took note of heavy users of alcohol of whom there was only a small number (7%). The beneficial effects of alcohol may be partly neutralised in the heavy drinkers by increases in blood pressure and sympathetic over-stimulation.[152]

3) **Cardiac Catheterisation and Coronary Angiographic Findings**

121 cardiac catheterisation procedures in total were performed, of which 93 were early (i.e. the indication occurring during the primary CCU admission and performed before discharge from hospital), giving an early catheterisation rate of 51.3%. Despite an expectant strategy of management with the option of active intervention, only 28 late cardiac catheterisations were done (i.e. the indication occurring only after discharge from CCU). This late catheterisation rate of 16.1% is noticeably lower than the 43% in the conservative strategy group of TIMI II which had a similar stated expectant management protocol as in the GSH Study, except that patients were randomised to this group on admission and underwent exercise stress testing before discharge.[22]

Complications related to catheterisation were uncommon, with no deaths, 2 aortic dissections (which were considered to be minor and successfully managed conservatively) and the requirement of one intra-aortic balloon pump following the provocation of ischaemic chest pain. This compares well with the previously reported 2-11% complication rate of coronary angiography performed early in NQMI.[75]

The coronary angiographic findings showed that occlusive coronary artery disease was present in 58% of patients who were catheterised. The culprit vessel or infarct-related artery (IRA), defined as the vessel that was most likely responsible for the regional wall motion abnormality (taken as signifying the site of infarction) observed in the LV

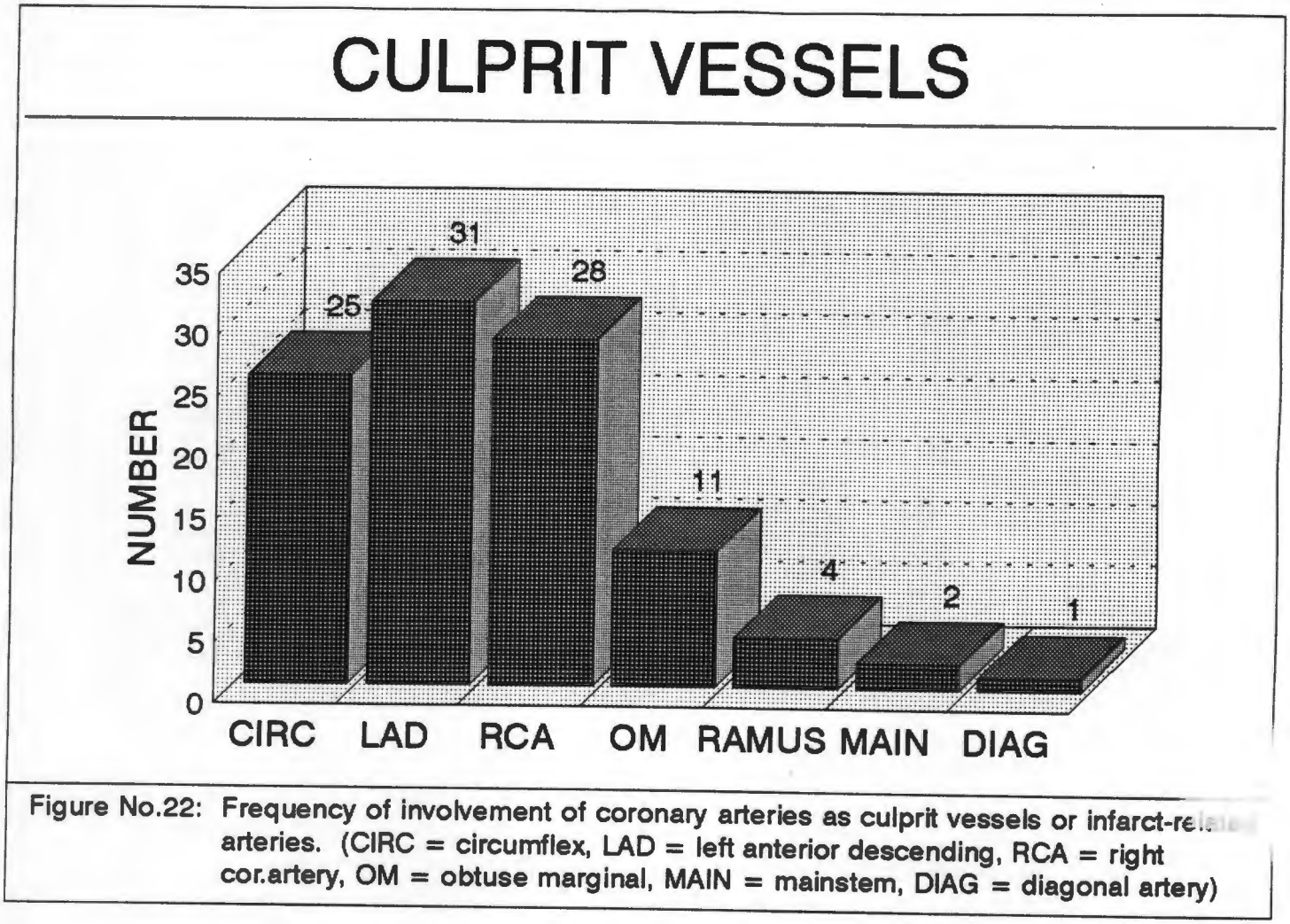


Figure No.22: Frequency of involvement of coronary arteries as culprit vessels or infarct-related arteries. (CIRC = circumflex, LAD = left anterior descending, RCA = right cor.artery, OM = obtuse marginal, MAIN = mainstem, DIAG = diagonal artery)

angiogram, was found to be occluded in 60.2% of the early and 32,1% of the late angiograms (p=0.009). (Occlusion was taken as functional occlusion or TIMI grades 0 or 1.) The left anterior descending arter (LAD), followed by the right coronary arter (RCA) and circumflex were most frequently involved (Figure No. 22).

IRA occlusion rates in NQMI are significantly lower than in QMI as discussed in the Introduction: Differences between QMI and NQMI. Results of individual studies vary from 23%[45] to a 48%[38] rate of IRA occlusion in NQMI. Extrapolation from nontransmural infarct studies show an occlusion rate of up to 51%.[43] No study compares exactly with another because of varying inclusion criteria and timing in relation to the index

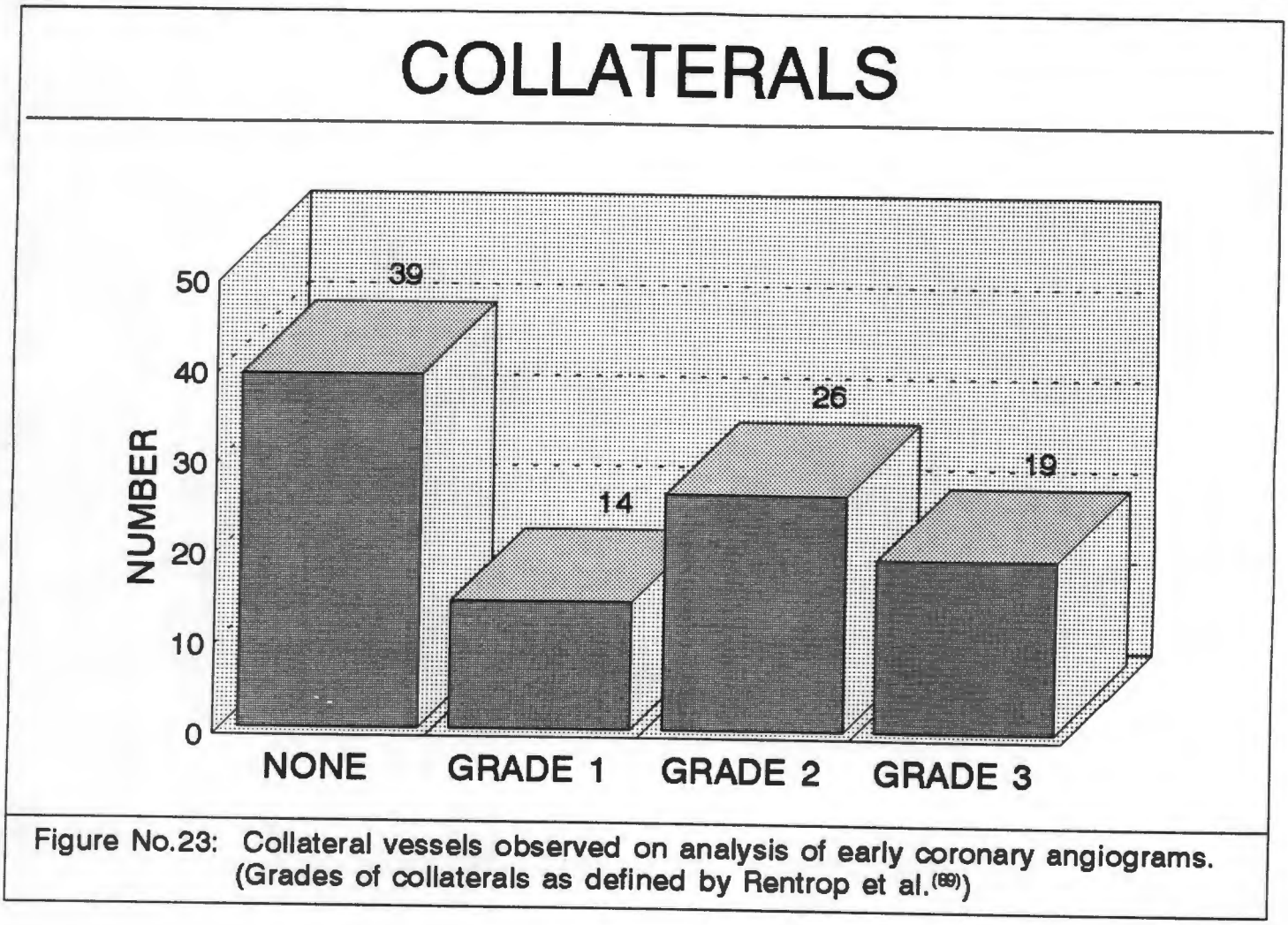


Figure No.23: Collateral vessels observed on analysis of early coronary angiograms. (Grades of collaterals as defined by Rentrop et al.[89])

NQMI. Even so, the IRA occlusion rate in the GSH Study is high. Among patients who had been given thrombolytics, the rate was 20%,whereas the TIMI II Study showed an equivalent occlusion rate of 11.1% in patients with NQMI.[22]

Collaterals in the GSH Study were present in 60.2% of all angiograms analysed: 60.4% of the early catheterisation and 75% of the late catheterisation group of patients had collaterals (Figure No. 23).

In an elaborate cross-sectional study by De Wood et al, of coronary angiographic findings soon after NQMI (341 patients) with catheterisation variably performed at <24 hours after peak symptoms, between 24-72 hours and between 72 hours and 7

days, total occlusion of the IRA was found in 26% (49 of 192), 37% (35 of 94) and 42% (23 of 55) of the patients respectively ($p<0.05$) and a parallel increase in the presence of visible collateral vessels in 27, 34 and 42% respectively ($p<0.05$).[75] A similar parallel, but with higher figures of 60% occlusion of IRA and 60% presence of collaterals, was noted in the GSH Study. It therefore appears that complete failure of perfusion is infrequent in NQMI.

Eighty-four percent of all angiograms analysed showed that perfusion was maintained by either collateral vessels or a patent IRA. Seventy percent of those with IRA occlusion had collaterals. This compares with De Wood's report that 85% of patients with NQMI and an occluded coronary artery, had collateral flow to the area distal to the occlusion.[75] Another study showed residual perfusion in 79% of patients during the first 6 hours of NQMI.[40]

The high IRA occlusion rate in the early catheterisation group of patients in the GSH Study may partly be explained by the timing of the angiography. Although indicated during the primary admission with the index NQMI to the CCU, and usually performed within 3-4 days, some of these procedures were only done into the second week of admission. De Wood's study showed an increasing total occlusion rate with time. A study by Gibson et al reported an occlusion rate of 53% in NQMI patients studied 11 ± 3 days after NQMI.[144] Also the GSH Study was heterogeneous, including first NQMI and previous MI, and not only asymptomatic patients, but those with ongoing or

recurrent chest pain/post-infarct angina in whom a higher occlusion rate may have been expected.

Despite these possible explanations, the findings still seem to be at odds with the belief that NQMI are due to transient occlusion (equivalent to QMI with thrombolysis). However, even when total occlusion was observed, perfusion of the distal vessel was almost always maintained by collateral vessels. The occlusion is not the important issue, the collaterals are. The essential finding of this study is that some degree of perfusion (either antegrade or by collaterals) is present soon after NQMI, sufficient to limit the extent of the initial necrosis.

The occlusion rate in patients in whom coronary angiography was indicated subsequent to discharge from CCU, had a lower rate of IRA occlusion. Unlike the two TIMI studies, where the majority of patients in the conservative strategy groups had what was considered failure of therapy and thereby reached the study endpoint soon after the index event (in TIMI IIIB the average time to catheterisation in the early conservative group was 7.1 days[68]), the patients in the GSH Study who had late catheterisation , had this procedure much later, (an average of 2.2 months). It is possible that they therefore represented a different type of coronary artery disease. NQMI has been shown to occur in patients with either minimal stenosis with an unstable plaque or in severe stenoses in multiple vessels.[41] In the latter, NQMI may simply represent a severe imbalance between supply and demand in the presence of a patent, but severely narrowed coronary

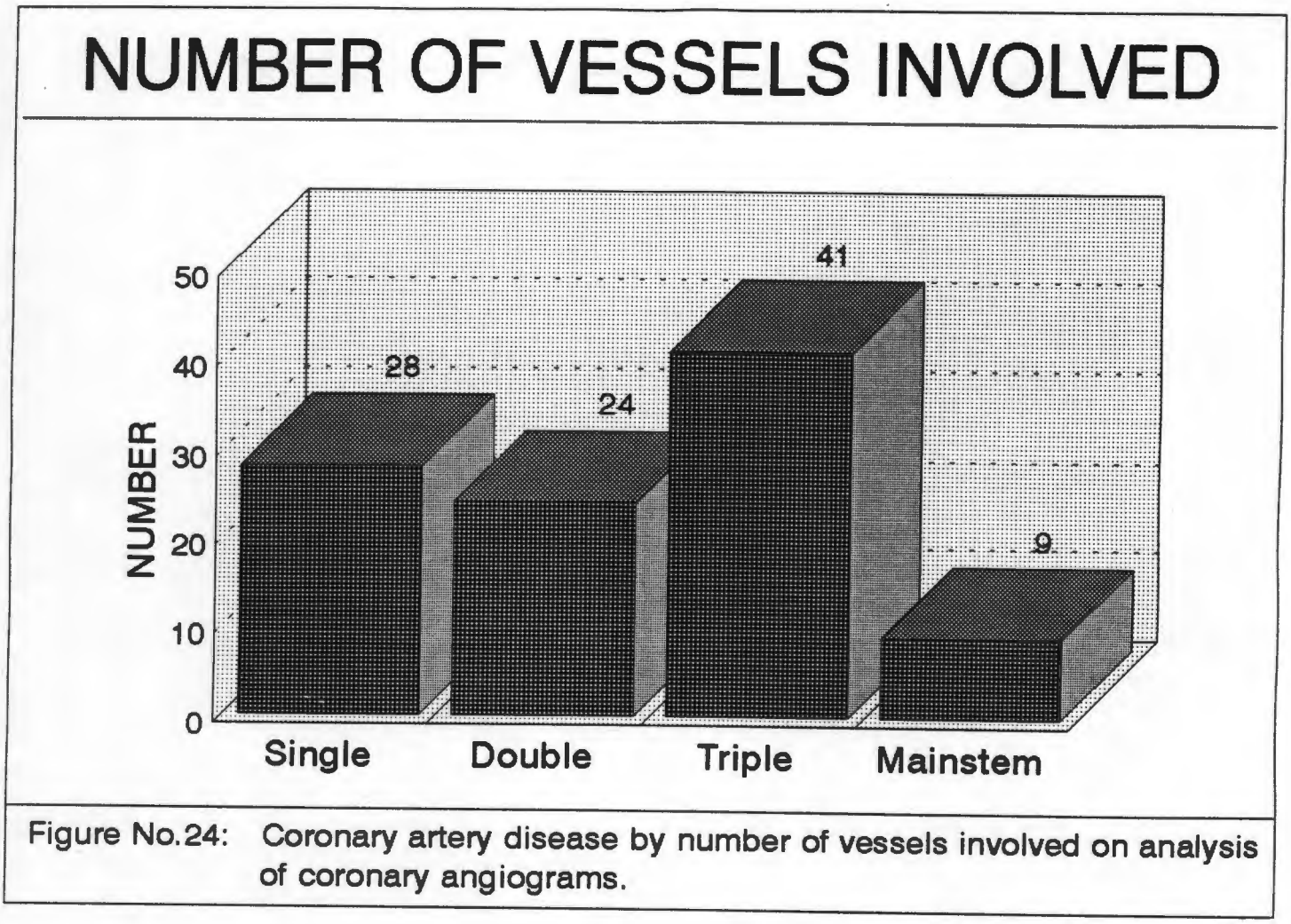


Figure No.24: Coronary artery disease by number of vessels involved on analysis of coronary angiograms.

artery.[75] The more acute recurrences noted in the TIMI studies may reflect the acute unstable plaque complications, whereas the late catheterisation group of the GSH Study may be due to progressive coronary artery narrowing in patients with severe multiple vessel stenoses. Unfortunately, such a theory is difficult to prove as angiographic data of the late catheterisations were not evaluated.

Assessment of coronary disease in the GSH patients showed that 72% had double-vessel coronary artery disease or more (Figure No. 24). (A similar assessment by Parikh et al of NQMI was 52%.[153]) The most frequently involved coronary artery was the left anterior descending artery (LAD). When culprit vessels were related to NQMI location, posterior and infero-

posterior NQMI were most frequently caused by circumflex, and inferior NQMI by right coronary artery lesions. In the TIMI II Study, the circumflex artery was classified as the infarct-related artery, more commonly in patients who evolved NQMI than in those with QMI:

NQMI 20.6% versus QMI 9.9% ($p<0.001$) [22]

Left ventricular angiographic findings revealed some wall motion abnormality in 85% of the GSH patients. Dyskinesia was noted in 6 patients and LV aneurysm in 4 patients. Bearing in mind the inclusion criteria in this study, it was inevitable that some patients undergoing cardiac catheterisation would have had previous MI. An angiographic study comparing NQMI and QMI showed that apical aneurysms occurred exclusively in patients with QMI.[48] Analysis of the 4 patients with LV aneurysm in the GSH Study revealed that they had all had previous MI.

4) **Thrombolysis and Incidence of NQMI**

Twenty-nine of the patients admitted to GSH over the 4 years, covered by this study, were given thrombolytic agents (28 streptokinase and 1 TPA). From 1990 through to 1993, the percentage of NQMI patients receiving thrombolytics increased progressively (9.4%, 11,6%, 15.4% and 24.1% in each of the successive years) (Figure No. 25).

Analysis of the annual number of acute MI eligible for inclusion in this study also shows a steady increase over this

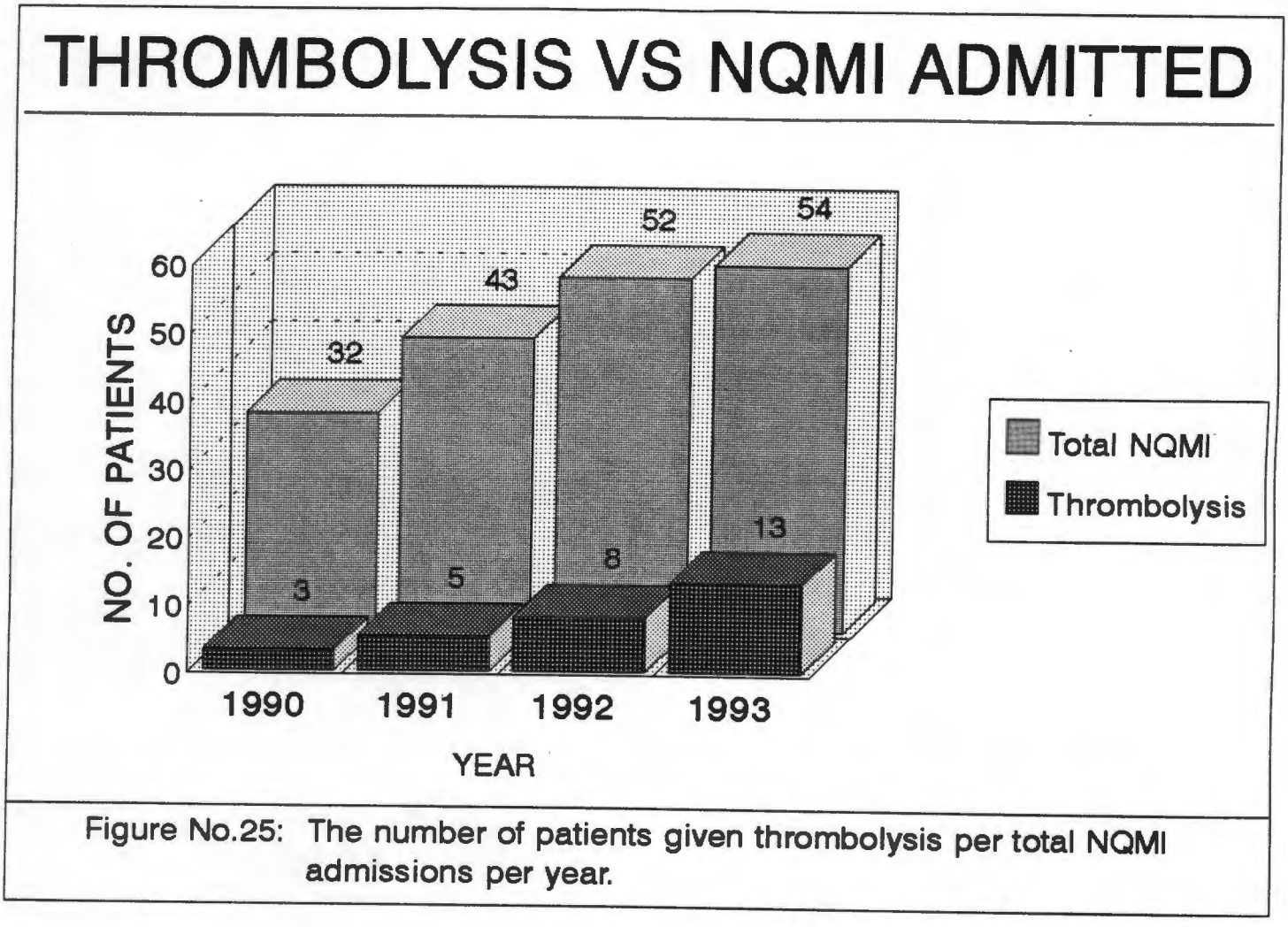


Figure No.25: The number of patients given thrombolysis per total NQMI admissions per year.

time period. A possible explanation for this may be the observed, more frequent use of thrombolytics.

In a study by Goldberg on changes in the occurrence and prognosis of NQMI, in the Worcester metropolitan area (USA), it was shown that there was an increase in attack rates of NQMI from 46 per 100 000 in 1975 to 89 per 100 000 in 1981 ($p<0.001$), a relative increase of 93% for NQMI, whereas the concurrent increase for QMI was 29%.[54] The increased frequency of NQMI was thought to be due to greater awareness of the diagnosis, patient education, better treatment of chronic IHD and modification of risk factors.[24] The increase in NQMI, especially those of small size, also reflected the improvement in sensitivity of MI detection.

Using the standard ECG algorithm, no increase in attack rates of NQMI between 1970 and 1980 was shown. However, when CPK and CPK-MB were considered, NQMI (or rather recognition of these infarcts) had increased.[154] Now it is the therapeutic interventions (Beta-blockers, nitrates and anti-thrombotics) capable of limiting MI extension, that seem to be responsible for the true increasing incidence of NQMI.[13] An alternative view of this, as proposed by Boden, is that thrombolytic therapy may be contributing to the expanding pool of patients with incomplete infarcts.[35]

The use of thrombolytics in NQMI patients may be criticised. The TIMI IIIB Trial assessing the effects of TPA in UAP and NQMI stated that the addition of a thrombolytic agent is not beneficial and may be harmful.[68] This study, however, was limited to patients presenting with ST segment depression. The recommendation, therefore, cannot be applied to patients who present with ST segment elevation. The beneficial effect of thrombolytic in acute QMI is well proved, and even though ST segment elevation is not an invariable harbinger of subsequent Q waves (in the TIMI II Study, 29% of patients presenting with ST segment elevation and given TPA sustained NQMI[22]), thrombolytics are strongly indicated.

5) **NQMI Location**

Location of NQMI, as determined by LV angiography, echo-cardiography, nuclear imaging, ECG characteristics of ST segment elevation or T inversion and coronary angiography, in

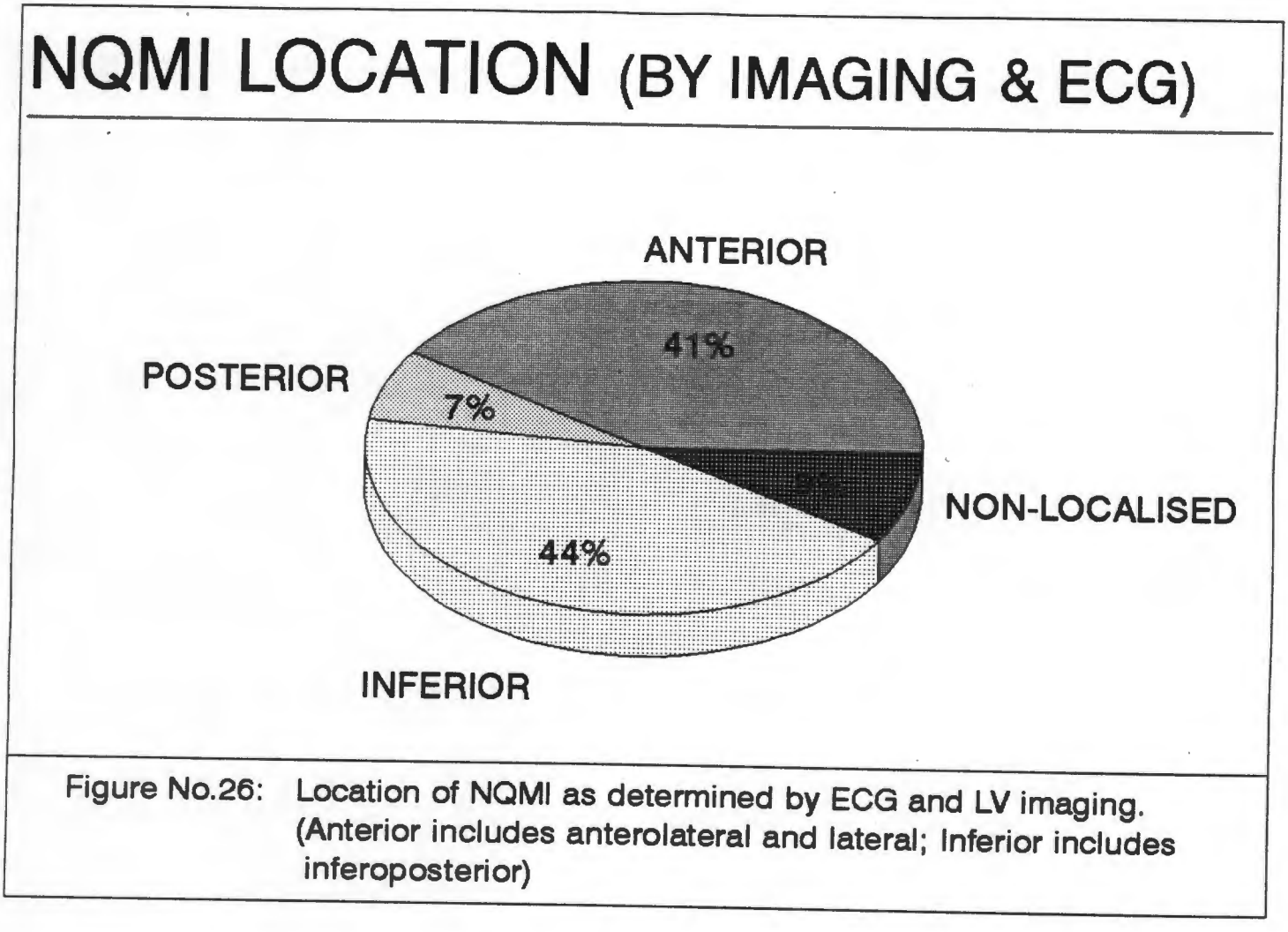


Figure No.26: Location of NQMI as determined by ECG and LV imaging. (Anterior includes anterolateral and lateral; Inferior includes inferoposterior)

diminishing order of preference or certainty, was (Figure No. 26):

44% inferior, 40% anterior, 7% posterior and 9% non-localisable.

Localisation just on the basis of ECG showed that:

34% were inferior, 40% anterior, 2% posterior and 22% non-localisable.

Although the "non-localisable by ECG" incidence at GSH approximates the rates in other studies (e.g. 19.3% in a study

by Schechtman et al[146]), the GSH incidence of anterior NQMI is lower than the 51-65% of these reports.[146][147]

The significance of this localisation is prognostic.[155] Using data from the Multicenter Investigation of Limitation of Infarct Size (MILIS)[146], Stone et al[156] suggest that long-term mortality among patients with anterior NQMI is more than twice the rate in inferior NQMI regardless of infarct size. The reason may be the major association between LV function and outcome after acute MI. Lower LV ejection fractions have been observed in anterior infarcts as opposed to inferior MI.[63] Hence the prognostic implication of infarct location remains valid even adjusted for infarct size or type of infarction.[34] It has however, been suggested that such data applies more specifically to the first infarct,[88] since in patients with previous MI, a new infarct in any location, superimposed on extensive previous infarction, may be enough to tip the balance regarding LV function and poor prognosis.

The study of Schechtman et al showed that infarct localisability implied increased risk. In the GSH study, non-localisable infarcts (even when LBBB was excluded) did not show lower mortality. This is not entirely out of keeping with Schechtman's view that non-localised NQMI defines a heterogeneous population, and although in his study these patients were associated with a lower mortality, they could not be assigned to a low risk stratum[146] (i.e. they may require an active interventional strategy).

Accumulated data does not favour the prognosis of inferior infarction over the anterior variety in QMI alone, but also in NQMI. Thus, inferior NQMI carries the "best survival". The Schechtman Study showed that the 1-year mortality was:

inferior NQMI 2.8% versus anterior group 17%.(146)

Patients with inferior MI have a prognosis that is generally so good that even the issue of thrombolytic therapy remains unsettled.(147)

In the GSH Study, survival benefits could not be shown for inferiorly located NQMI. However, a statistically significant association was made with a lower incidence of early recurrence of symptomatic ischaemia.

In view of the high post hospitalisation risks and increasing frequency of NQMI, it is important that characteristics such as infarct location distinguishing low and high risk patients be defined. Accurate risk stratification is the basis for differential, yet successful post-infarct management.

2. ECG LOCALISATION OF NQMI

The importance, especially with regard to prognosis, of establishing the site of location of a NQMI, has been discussed. In the previous section, the method of infarct localisation was by imaging of the LV invasively (e.g. LV angiography) or by echo-cardiography or radionuclide scanning. Knowledge of the accuracy of ECG method of localisation is crucial before suggesting that

NQMI infarct location as determined by the 12-lead ECG, should be used as a major risk stratification factor. If the ECG method is found to be unreliable, use of the other modalities of localisation may be warranted. These would add to patient management costs and strengthen the argument in favour of invasive investigation/ intervention in all NQMI as being the most cost-effective method in the long-term.

Difficulties exist in correlating pathological/anatomical location with ECG location as postmortem studies have shown a high incidence of multiple/previous infarcts in NQMI patients that have died after the acute event.[43] Furthermore, NQMI presenting in a relatively silent way and especially first time NQMI, which has been shown usually to be a small infarction with good LV function, is unlikely to cause death or come to postmortem. Therefore, in order to assess the value of 12-lead ECGs in localising NQMI, only first infarcts can be evaluated and other reliable methods of localisation for comparison, are required. For this, angiography has been used as a gold standard. Unfortunately, it too has drawbacks. As has been shown in this GSH Study, regional wall motion abnormality, seen on LV angiography and used to identify the location of the NQMI, is not seen in 15% of patients undergoing this investigation. This is not unexpected as it reflects small infarction that is not detectable by this method. This is not a significant problem, as these types of infarct probably do not affect prognosis.

2A. <u>ECG FOR LOCALISING NQMI TERRITORY</u>

Using the most severe electrocardiographic changes (as described previously in Study Methods, with ST segment elevation, and T wave

inversion in order of decreasing validity), NQMI locations as determined by ECG in this study were (in groups):

- anterior (and lateral) 42%
- inferior 34%
- posterior 2%
- non-localised 22%

In applying various epidemiological tests comparing 12-lead ECG and angiography (which is taken as being the gold standard despite minor reservations) for the localisation of only first time NQMI, the above-mentioned methods (ST segment elevation or T inversion) of localisation of infarcts that do not have Q waves show an overall positive predictive value of 61% for all NQMI infarcts or 70% if only localisable NQMI are considered. (This positive predictive value of ECG varied, from 87% for the inferior group of NQMI, 63% for the anterior and 19% for ECG non-localisable infarcts.) The overall sensitivity for any of the specific 4 groups of locations was 56% and the specificity 88% (i.e. specificity in defining the location within the total NQMI group and not NQMI versus non-NQMI). The sensitivity of 18% in diagnosing posterior MI, confirms previous findings that the ECG is an extremely non-specific localiser of posterior infarction.[157]

2B. ECG FOR DETERMINING SPECIFIC NQMI LOCATION

More specific localisation of infarction (within groups), e.g. inferior, infero-posterior, infero-lateral, anterior, anteroseptal, anterolateral, is described in ECG texts by Schamroth[129] and Rowlands.[130] Various NQMI studies including the TIMI II Study determine this specific location by the extrapolation of the rigid

electrocardiographic criteria set down in the WHO categorisation (1959) and the Minnesota Code (1969), despite the fact that these criteria originally required 2 contiguous Q waves for the ECG diagnosis of acute infarction.[74] The Multicenter Post-Infarction Programme (MPIP) has set specific NQMI criteria for all locations (obviously except for posterior NQMI because ST - T changes in V_1 - V_2 in the absence of a tall R wave are considered to be anterior).[74] The GSH Study shows that this more specific localisation of NQMI is of poor value. Although for infero-posterior infarcts the ECG had a positive predictive value of 100% for angiographic evidence of this location of infarct, the sensitivity was very low at 7%. The overall, positive predictive value (for all specific locations) was 29% and specificity 25%.

2C. SPECIFIC COMPONENTS OF ECG FOR LOCALISATION OF NQMI

Fuchs investigated the accuracy of the 12-lead ECG in localising the site of the coronary artery narrowings as documented with single vessel disease on angiography.[131] Q waves, ST segment elevation and T wave inversion in leads I, aVL and V_1 to V_4 were all highly correlated with LAD disease and in leads II, III, aVF with right coronary artery (RCA) or circumflex disease ($p<0.001$). The location of new T wave inversions on the resting ECG during MI was found to be useful in predicting the site of coronary artery disease. ST segment depression did not accurately reflect the site of ischaemia because it occurred frequently both as a primary change due to "subendocardial" ischaemia or infarction and as a secondary "reciprocal change" as substantiated by animal experiments. Fuchs showed that:

- Q waves identified the location of coronary artery disease in 98% of cases
- ST elevation in 91%
- T inversion in 84%
- ST depression in 60%

Review of his data shows that 37 of the 42 patients with ST segment depression had simultaneous ST elevation in other leads. Hence the statistics do not really assess the value of ST segment depression alone. Other studies have also shown the only moderate value of the ECG repolarisation changes. De Wood found that about 50% of patients with NQMI had anterior ST-T changes even though the LAD was not involved.[30]

In analysing the GSH data, the overall (positive predictive) value of the specific components of the 12-lead ECG in predicting angiographic location of NQMI was:

- ST segment elevation 79%
- T wave inversion 50%
- ST segment depression 48%

Thus, only ST segment elevation in either the anterior or inferior leads and possibly T wave inversion combined with ST segment depression (in the inferior leads only) have any value in localisation of NQMI by 12-lead ECG. ST segment depression alone is confirmed to be of no value.

These figures are worse than in Fuch's Study[131] which may have been expected to show poorer correlation given the interpatient

variability in coronary artery supply against which the ECG was being evaluated in his study. In addition, these results question the validity of studies (e.g. those assessing the mortality and NQMI location[146] and sites of NQMI reinfarction[93]) where infarct location is determined by ST segment shifts (either way).

Other methods of ECG analysis which emphasize the presence of diagnostic information outside the initial part of the QRS and/or signal processing using T waves and QRS voltages which have been shown to be useful in differentiating between Q and NQMI,[158] have not yet been evaluated with regard to localisation.

2D. SIGNIFICANCE OF COMPONENTS OF ECG IN NQMI

Analysis of the ECGs of the patients included in the GSH NQMI Study showed:

- ST segment elevation in	97 patients	(54%)
- ST segment depression in	52 patients	(29%)
- T inversion (excluding ST segment elevation) in	62 patients	(34%)
- ST segment depression (excluding T inversion) in	11 patients	(6%)

Other NQMI studies have shown that the prevalence of early ST segment elevation in NQMI is 30-43%.[41][46][35]

Although ST-T changes, particularly ST depression, are inaccurate for locating NQMI, they may be useful for prognostic purposes. Ogwawa et al, who studied the ECGs obtained within 12 hours of the onset of NQMI, found that patients with ST segment depression in

any leads had a higher rate of multivessel disease and mortality.[137] Not only ST segments, but T waves provide very early and valuable prognostic information. In a study of 911 men with UAP or NQMI, the ECG during the initial hospitalisation was associated with the following prognosis:[82]

- Normal ECG:	8%	1 year risk of MI or death
- Isolated negative T waves:	14%	($p<0.05$)
- ST segment elevation:	16%	($p<0.05$)
- ST segment depression:	18%	($p<0.01$)
- Combination of ST elevation and depression:	26%	($p<0.001$)

Changes noted in serial ECGs (not just on one-off ECG analysis as above) may be even more valuable. Using the Diltiazem Reinfarction Study database, it was shown that persistent ST segment depression appeared to be the marker for poor outcome. Patients with ST segment depression on admission and at discharge experienced a 22% 1-year mortality. Those without ST segment depression had a 5.5% mortality.[108] ST segment depression predicts more than just mortality. LV function has been noted to be significantly lower in NQMI patients with ST segment depression.[18] This may be due to the higher frequency of previous MI in these patients[159] and the reason for their higher mortality.

In the GSH Study, widespread ST segment depression was associated with greater instability in the immediate outcome of the patients admitted with NQMI. No statistical association was noted in relation to recurrence of ischaemia or mortality, even on subanalysis (previous/first NQMI).

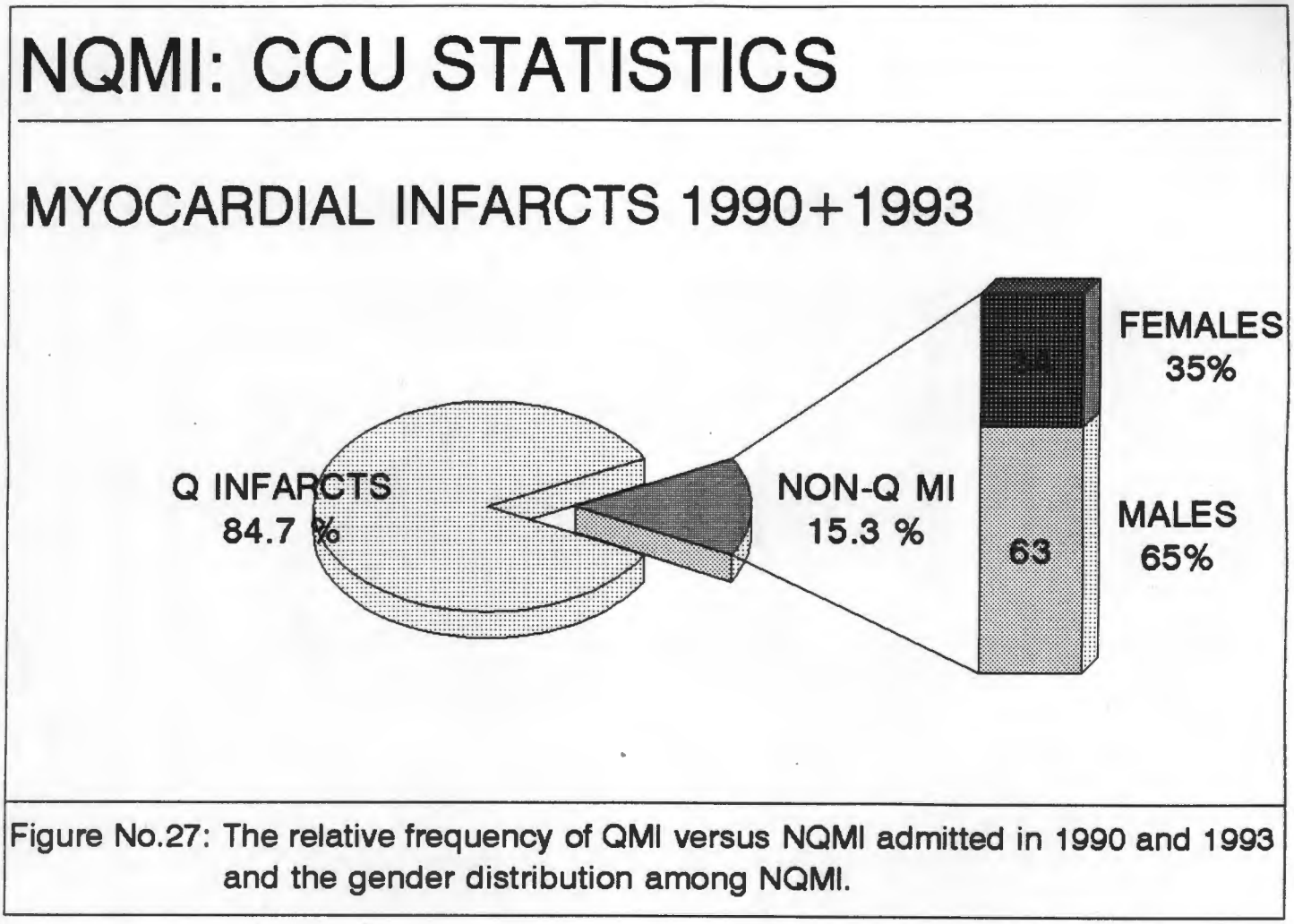


Figure No.27: The relative frequency of QMI versus NQMI admitted in 1990 and 1993 and the gender distribution among NQMI.

The greatest value of the ECG in risk stratification is therefore in determining the lower risk categories: viz. normal ECG, no ST segment depression and inferior location of NQMI as determined by ST segment elevation alone.

3. COMMENTS ON GSH CCU STATISTICS

3A. NQMI VERSUS QMI RATE

The NQMI rate for the GSH CCU was determined for 1991 and 1993 and found to be 13% and 17% respectively (Figure No. 27).

The reported rate of NQMI is very variable - from 29% in the Multicenter Diltiazem Post-Infarct Trial[50] to 52% amongst 921 patients with acute MI admitted to Goteborg Hospital in Sweden.[25]

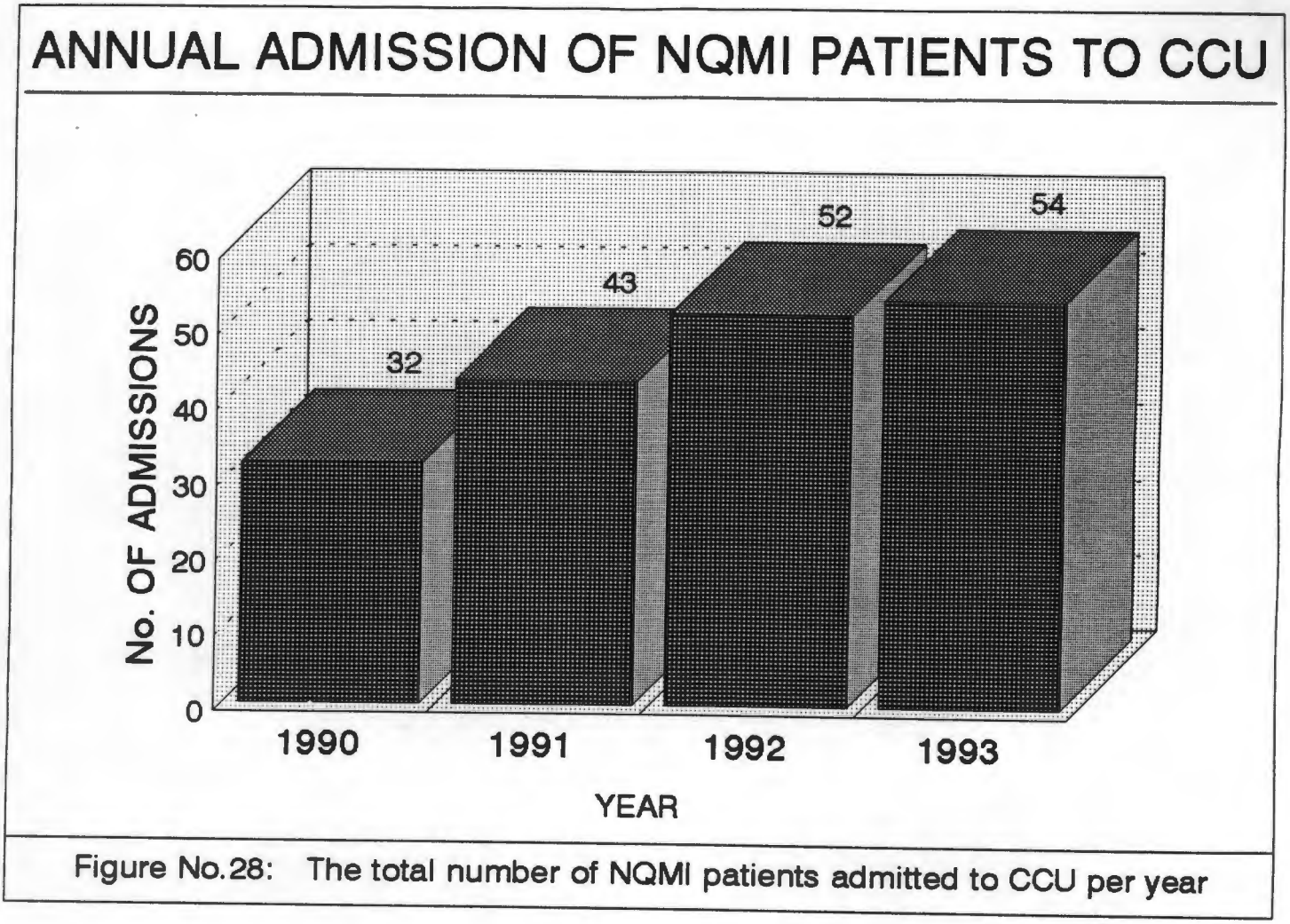


Figure No.28: The total number of NQMI patients admitted to CCU per year

Much of this variation is dependent on the time of the ECG used to classify acute MI into either Q or NQ. Most classifications in the past were done at the time of discharge from hospital, giving ample time for Q waves to evolve. It was assumed that Q waves appearing late were all part of the initial assault on the heart. This assumption may be incorrect. Other studies have used the admission ECG e.g. TIMI IIIB. TIMI II used the day 2 ECG since this was considered the time most physicians made clinical decisions concerning the necessity for catheterisation in stable patients.(22)

In the GSH Study, all records from the CCU were studied retrospectively. These included the series of ECGs on admission to determine NQMI location and also the pre-hospital discharge ECG

(provided that the patient remained stable in the interim) to exclude the presence of Q waves. If these had evolved late (without any evidence from history and ECG of recurrence of ischaemia), the patients were excluded from this study. In a study of patients with NQMI by Kleiger, analysis of the ECG at 50 ± 10 hours after the acute event showed subsequent late evolution of Q waves in 14% of patients.[66] This group was more likely to exhibit ST segment elevation ≥1mm and have higher CPK values. This progression to QMI appears to involve two different mechanisms:

1. temporal lag in ECG; and
2. actual extension.

Another study in patients who received thrombolytics relating the timing of Q wave evolution to prognosis, showed that delayed Q development (>3 hours after starting thrombolytic therapy) was similar to NQMI with respect to lower CPK peak, better LVEF, less cardiac failure by discharge and lower in-hospital mortality than the QMI group.[73] Thus, excluding all those patients with even later Q wave extension in the GSH study, may have been incorrect. The numbers of patients thus affected was not determined. Eisenberg et al reported that progression of NQMI to QMI occurred only in 1.5% of patients treated with thrombolytic therapy in the period from 24 hours after the onset of the index event to hospital discharge.[73]

3B. TIME DELAY: ONSET TO TREATMENT

In a study determining the clinical features of patients given streptokinase and developing either NQMI or QMI which occurred in 43% and 57% respectively, the time from symptoms to thrombolytic

treatment averaged less than 3 hours.[46] This contrasts quite markedly with the time delay, from onset of chest pain to arrival at hospital, which averages to 7.1 hours for the GSH patients. This does not include substantial delays which do occur in the emergency unit and before any treatment is given. This may also account for the relatively small number of NQMI patients, especially in the thrombolytic era, as Q waves may have developed during this long time delay, well before any thrombolytic is administered. Also of note is that the duration of chest pain on average is 4 hours and that this therefore is frequently no longer present by the time the patient arrives at hospital.

In a review by Jenkins et al, of the causes of higher in-hospital mortality in women than in men after acute MI, the times (in the early 1990s in Missouri, USA) from chest pain to emergency room were 5.3 $\pm$ 12.7 hours for men and 8.9 $\pm$ 19.9 hours for women ($p=0.03$).[149] In the GSH Study, this male to female ratio was reversed, with the time for men being 8.25 $\pm$ and 10.4 hours and for women being 4.73 $\pm$ 3.3 hours (p=NS). There is no obvious medical or sociological reason for this. No statistical difference could be found between male and females in mortality or immediate post-infarct course. One may, therefore speculate whether, in the GSH Study, the earlier arrival of women was somehow associated with the neutralisation of their usually worse outcome.

The duration of admission of NQMI patients to the GSH CCU was for a mean of 3.66 days (range 1-11 days). This, with the 1993 total admission reaching 791 in a unit with just 10 beds, reflects a high turnover of patients. Despite this, the incidence of poor immediate outcome and in-hospital mortality was low.

3C. ASPIRIN

Aspirin (daily, in antiplatelet/antithrombotic doses) was being used by 14.9% of the GSH patients prior to the index MI. This contrasts with the TIMI IIIB Study where half the patients had taken aspirin within 24 hours of admission.[68] Eighty-five percent of the patients in the GSH Study were discharged from CCU on aspirin which leaves a larger number than expected not on aspirin. The most frequent reason for this appeared to be aspirin intolerance. Aspirin use after infarction was associated statistically with, but was not an independent predictor of lower, early recurrence of symptomatic ischaemia.

3D. BETA-BLOCKER

Beta-blockers were used by 24% of patients before and by 70% after the primary admission with the NQMI. The relatively high pre-index MI use of beta-blockers reflects the 48% prevalence of hypertension and 50% of previous ischaemic heart disease in this study population. As shown in the section Results, the prior use of beta-blockers before the index NQMI did not influence significantly the outcome or subsequent mortality. Beta-blocker use after the index NQMI was statistically associated with a reduced total and cardiac mortality.

Another interesting association is that of reduced total subsequent mortality in the group of patients who were unstable immediately post-infarct and given beta-blockers as compared to those not on this drug ($p=0.014$). No direct effect can be inferred from this as the tolerance of beta-blockers may be a marker for improved survival.

Review of the presence of pre-admission risks shows that the prevalence of certain factors is, as expected, higher in NQMI patients than is usually found in the general population e.g. hypertension in 48%, diabetes mellitus 19.3%, known previous hypercholesterolaemia 12%, but on admission 8%, and smoking 65%.

3E. CPK ENZYME

The median CPK value was 688. No significant difference was noted between the patients given thrombolytics and the group not given these agents. The results of CPK-MB isoenzyme testing were only available in 13 patients (7.2%). Although this is reportedly done on all admissions, the results did not appear to have been transcribed into the patients' notes. Since the diagnosis of NQMI required the triad of: symptoms, ECG changes and CPK elevation, the unavailability of the CPK-MB fraction, which is then mainly used in diagnostically doubtful cases, is unlikely to have changed much. It has been shown that CPK-MB isoenzyme may be elevated in the presence of normal serum CPK levels in NQMI.[142] Since the GSH chemical pathology laboratory does not give absolute measurements of MB isoenzyme and only calculates a fraction or percent of the total CPK if the latter is raised, these types of patients would not have been picked up at GSH. Furthermore, it has been recommended that blood samples for CPK levels be taken at 4-6 hour intervals for 18-24 hours, especially in NQMI[88] because the rise may be low and short-lived[33] because of early "washout". At GSH, CPK levels were done either at 12 or 24 hour intervals, thus non-sustained elevations in CPK would not have been detected and NQMI in such patients would have been missed. These patients would then have been labelled as having UAP. This too may account for

the somewhat lower proportion of NQMI among all infarcts at GSH as compared to other studies.

4. GSH CCU MANAGEMENT OF NQMI

Criticism of the CCU management of NQMI, as an audit of the practised management strategies, is valuable. However, it must be constructive as the achievements of the CCU in managing unstable patients and maintaining an almost negligible in-hospital mortality are commendable.

The routine management of patients admitted with the "acute coronary syndrome" (i.e. acute MI or UAP) follows generally accepted strategy, viz. bedrest and monitoring, oral aspirin, IV heparin and beta-blockers were possible. Heparin was administered in 89% of the patients. As to why this was not higher is unclear. Bleeding disorders may have accounted for a proportion of these. The protocol itself, of the administration of heparin, can also be criticised. The failure to monitor anticoagulation levels achieved by the standard dose of 25 000u of heparin per 24 hours and failure to give a bolus dose of heparin on admission as was the practice during the 4 years of this study, may have resulted in poor antithrombotic activity in all the patients in the first few hours after admission probably the most unstable and crucial time period, and in some of the patients in the succeeding 48-72 hours. This may have resulted in the extension of the acute MI. Bearing in mind the pivotal role of platelet aggregation in the pathogenesis of NQMI, the new antiplatelet agents may have a significant role during this initial time period.[79]

In the TIMI IIIB Trial studying patients with UAP and NQMI, all patients were given beta-blockers (metoprolol 50mg bd), a calcium antagonist (diltiazem 30mg 6 hourly) and a long-acting nitrate (isosorbide dinitrate ≥10mg 8 hourly).[68] This is unlike the GSH practice where only beta-blockers are given routinely. Since the practice of medicine at GSH is guided by the principles of evidence-based medicine, calcium antagonists are generally not used in acute infarct patients. None of this study's patients were given diltiazem. The result of giving nitrates and diltiazem to all patients in the TIMI IIIB Study may have been to mask some initially unstable patients. Alternatively in the GSH Study, since these drugs were not routinely given, it is more likely that patients with ongoing ischaemia became evident in hospital, during the primary admission, and were investigated. Thus the group of patients who ended up being treated conservatively, were completely "unmasked", and hence, of lower risk. Yet, with regard to recurrence of ischaemia, this lower risk, conservatively managed group was shown to have a result worse than the actively intervened patients.

The major criticism of the CCU management is the minimal use of the exercise stress test (EST) in patients admitted with NQMI. This test is often considered to be a routine pre-discharge procedure and an important method of risk-stratifying the potentially unstable group of NQMI patients. Only 9 of the GSH patients underwent EST, which was positive in 6. The use also, in the majority of these patients, was not to assess risk and thus determine subsequent conservative/active management, but to establish whether revascularisation was to be recommended in patients who had already undergone active investigation with

majority of these patients, was not to assess risk and thus determine subsequent conservative/active management, but to establish whether revascularisation was to be recommended in patients who had already undergone active investigation with cardiac catheterisation with equivocal stenoses on angiography. EST in the group managed conservatively may have altered the final outcome in this GSH Study, giving no advantage with regard to reduced recurrence of ischaemia to the initially active strategy and therefore a result similar to the two TIMI studies discussed previously. Thus, in the GSH Study, patients retrospectively categorised as having received conservative treatment, were truly managed conservatively.

5. LIMITATIONS/SHORTCOMINGS OF THE STUDY

The most obvious limitation of this study and therefore, of its conclusions is the fact that it is a retrospective/observational analysis. However, even this type of review has some value, particularly as an audit of management practice and as grounds on which a prospective trial could be based.

A shortcoming may be the patient population studied. Some selection bias inevitably took place for admission to the CCU rather than to the medical wards. Thus, this group of patients included in this study may not be truly representative of the entire spectrum of NQMI patients. Even though these study patients may have been relatively more unstable, the in-hospital mortality rate remained low. Deaths prior to admission to CCU may have been due to NQMI, but were excluded from this analysis possibly also making this in-hospital mortality rate falsely low. Any

prospective study on NQMI patients, in order to reflect the entire heterogeneous group, should therefore include all such patients admitted to the hospital.

Including all patients admitted to hospital with NQMI in a study may overcome the other shortcoming of the total number of patients in the study. To achieve some statistical significance, sufficient patients had to be included in this analysis. This could only be done by including patients over the relatively long period of 4 years. This poses difficulties with the rapidly changing practices and advances in management of modern cardiology.

Results and conclusions of a study such as this are limited by the non-uniformity within groups compared. The various or non-uniform indications for active intervention limit the interpretation of this strategy being generally recommended. Perhaps uniformity in a group of patients as heterogeneous as NQMI is an impossible goal.

6. SUGGESTED FUTURE STUDY

It has been said that until it is broadly accepted that low-risk subgroups can be prospectively and non-invasively identified, the suggestion that all patients with NQMI should undergo coronary angiography will retain wide acceptance.[146]

The results of this retrospective GSH Study, justify the conduction of a randomised study. Such randomised clinical trials are particularly important when the plausible effect is only moderate e.g. 15-25% reduction in the risk of developing a major adverse outcome such as death or reinfarction in NQMI patients.[104]

Since the incidence of subsequent coronary events is high among NQMI patients, an opportunity is provided for objective assessment of the efficacy of various treatment. Moreover, studying a high risk subset such as this has the advantage of being able to show benefits after a relatively short time period and having clearly identifiable endpoints.

Such a proposed study would be similar to the TIMI IIIB i.e. a comparison not of invasive versus non-invasive, but rather of 2 management strategies: routine early coronary angiography and revascularisation versus conservative treatment with angiography available if medical management fails.

By means of statistical formulas, the number of patients needed for such a study on NQMI can be calculated based on this study's retrospective findings of a 37% occurrence of recurrent ischaemia in the active strategy group versus a 62% occurrence in the conservatively managed patients (as summarised in Figure No. 18). The total number of patients needed in a 1:1 randomised study to show a risk reduction of 25% with various significance/confidence levels and statistical powers, is as follows:[160]

Confidence	Power	Sample Size Test
90%	80%	110
95%	**80%**	**136**
99%	80%	176
95%	90%	176

Obviously, larger trials would be needed to show survival benefit as the mortality rate is low in NQMI patients.

A prospective study looking precisely at the question of NQMI management, in a way similar to the GSH review, has been embarked on. The Veterans Affairs Non-Q Wave Infarction Strategies In-Hospital (VANQWISH) Trial is a prospective, multicentre clinical trial which is testing invasive versus conservative strategy (cardiac catheterisation only for post MI angina or significant inducible ischaemia) in the early post-NQMI period, the purpose of which will be to compare the effects of these management strategies on long-term (minimum follow-up: 1 year; median follow-up 2.4 years) clinical outcome (all-cause mortality; recurrent non-fatal infarction).[108] Over 900 patients are to be recruited. The Data Safety and Monitoring Board has recently (August 1995) approved that the study, begun in May 1993, be continued until completion. This may indicate that on the basis of cumulative data available on over 800 patients so far recruited, there may be no significant differences, although to date, there appear to be more events in the invasive arm. Interestingly, only approximately 30% of the patients who have been randomised to the conservative arm have undergone a protocol-eligible cardiac catheterisation (personal communication: Boden - Chairman VANQWISH Trial). This is in contrast to the TIMI IIIB NQMI subset which showed that high percentage of conservatively managed patients (64% by 6 weeks) had crossed over to cardiac catheterisation and revascularisation.[68]

An abstract submitted to the 68th Scientific Sessions of the American Heart Association in November 1995 by the VANQWISH Trial investigators, analysing 726 patients, reveals clinical variables

similar to the GSH Study: 40% of the NQMI patients have ECG ST segment depression, 32% had anterior NQMI, 44% prior MI and 13% received thrombolysis. The result of the VANQWISH Study is therefore eagerly awaited. A more limited prospective single centre study may also give valuable information.

7. RECOMMENDATION: CONSERVATIVE VERSUS INVASIVE

The results of the GSH Study, albeit a retrospective one, appear to justify a more aggressive diagnostic approach. With this may be included a careful non-invasive search for ischaemia and often coronary angiography even in the asymptomatic, but selected patient.

1) **Medical therapy:**

In patients with NQMI, the only therapy of proven benefit for short-term cardioprotection is aspirin and perhaps diltiazem.[62]

2) **Stress Testing:**

Exercise stress testing should be performed at discharge and should probably be symptom limited. Since the recurrence rate early post-MI is so high in the first two months, it is not appropriate to delay the EST until a follow-up clinic appointment 4-6 weeks after the index NQMI. Symptom-limited exercise tests performed before hospital discharge after uncomplicated MI have been shown to provide significantly greater cardiovascular stress than do low level tests and are associated with an ischaemic response nearly twice as frequently, and are safe.[116] (The prognostic significance

of a positive response at higher work loads has not been identified.) EST use can also be selective. It has been shown to be particularly useful in patients with clinical markers of higher risk (e.g. pulmonary congestion) and of a more limited role in uncomplicated NQMI.[119]

3) **Alternative non-invasive tests:**

In those patients who have not had recurrence of ischaemic symptoms or angina at low levels of activity (i.e. where there has been no conventional indication for cardiac catheterisation), or who are unable to exercise additional means of risk identification may be required to predict future prognosis and intervene if the risk is considered unacceptable. Such tests include: thallium and sestamibi exercise tests and dobutamine stress echocardiography. Gibson et al suggest that asymptomatic patients who are then shown by these tests to have residual myocardial ischaemia especially in the area supplied by the LAD, should be considered for early coronary angiography.[144] However, no prospective study has yet demonstrated a reduction in the risk of MI.

There may be uncertainty regarding positive results. On the other hand, patients with negative maximum thallium exercise tests are, according to a prospective study, at very low risk of cardiac events in the 12-15 months post NQMI.[161]

4) **Invasive investigation and revascularisation:**

According to guidelines for early management of patients with acute MI set out by the American College of Cardiology /

American Heart Association Task Force, NQMI should be identified and studied during days 2-5 (phase 2) after admission.[162] Patients with jeopardised myocardium must be identified for revascularisation to try to improve survival. The problem with this is that any recommendation in favour of catheterisation of asymptomatic post-infarction patients assumes that prophylactic revascularisation will prolong life or prevent reinfarction. The evidence-based policy followed by GSH, is that in QMI and angina pectoris patients,[163] if a lesion is demonstrated, action is indicated only if symptoms occur. This should probably apply to NQMI also.

Routine cardiac catheterisation after 18-48 hours of anti-thrombotic therapy has a number of advantages:[68]

- rapid establishment of definitive anatomic diagnosis
- the ability to stratify prognosis
- a therapeutic plan can be developed.

One would therefore, be able to identify rapidly, either patients without critical obstruction who will not need revascularisation and should have a favourable prognosis, or patients with left mainstem or triple-vessel disease with LV dysfunction, in whom CABG has been shown to prolong life.[164][122] Revascularisation of other patients with critical stenosis, while not necessarily life-prolonging, may reduce the need for an anti-anginal medication and early re-hospitalisation. Thus, the definitive diagnosis and often definitive therapy, can be completed within several days of admission.

Routine catheterisation must be balanced against the following:

- NQMI has a more unstable pathology which is dynamically changing. The angiographic result is therefore, not definitive.
- Clinical features and EST should be able to identify most patients with prognostically important residual ischaemia.
- Many unnecessary revascularisation procedures may be performed if the cardiac catheterisation is used alone to determine the need for myocardial revascularisation.
- NQMI is a highly heterogeneous group with only some having an "incomplete infarction". A large minority (30-40%) have a very good prognosis subsequently.[62]

5) **Conservative treatment:**

Since trials, such as the TIMI IIIB, showed that the more conservative approach is equally acceptable and does not increase the risk of death, and results of definitive prospective studies[108] are not yet available, the conservative strategy cannot be regarded as incorrect management. However, it requires careful observation of the patient, identification of patients with residual ischaemia and the ability to go on to invasive management if medical treatment fails. This conservative strategy may require more medication, non-invasive testing and hospital admission.[68] Thus, in effect, it is not conservative treatment, but rather expectant. A substantial group of the GSH conservatively managed patients remained perfectly stable. This raises the issue of the cost/benefit ratio. If aggressive/interventional

management was the general routine policy, these patients would have all be catheterised, with cost, possible morbidity and complications.

6) **<u>Final recommendations:</u> NQMI management policy:**[165]

a) Antiplatelet therapy (and possibly short-term diltiazem) as soon as the diagnosis is established (probably excluding the patients with LV dysfunction).

b) Patients who develop early recurrent ischaemia on therapy (i.e. angina with associated ST-T wave changes) should undergo prompt cardiac catheterisation and myocardial revascularisation.

c) Patients with an entirely uncomplicated hospital course and who are asymptomatic require pre-discharge risk stratification. If they cannot be stratified by clinical or ECG characteristics (e.g. non-inferior NQMI), EST is required (preferably with an imaging study). If a high risk is shown, pre-discharge cardiac catheterisation is required.

The important consideration in management of NQMI is that this group is highly heterogeneous. The separation into Q and NQ following first MI may be artificial as studies have shown no real differences in mortality and reinfarction (in the longer term). Recommendations with regard to cardiac catheterisation and EST may at face value apply equally to both Q and NQMI patients, and this is regardless of whether patients receive thrombolytic therapy.[63] However, even this generalisation is "dangerous" as NQ myocardial infarcts form too heterogeneous a group to attempt to characterise, or confine, to one set of pathologies, prognoses or managements.

CONCLUSIONS

* NQMI managed at Groote Schuur Hospital Coronary Care Unit showed low mortality rates (particularly early in-hospital).

* Mortality is linked to recurrence of ischaemia requiring early re-admission.

* There is a high recurrence of ischaemic events after NQMI with the majority occurring within 3 months.

* If no recurrence of ischaemia occurs by 3 months, the likelihood of later recurrence is small.

* Retrospective analysis appears to relate active interventional management with a reduction in overall recurrence of symptomatic ischaemia.

* NQMI not localised in the inferior territory is associated with higher risk.

* ECG is of limited use in localising NQMI - ST segment depression is confirmed to have no localising value.

These findings may therefore, justify further risk stratification in the management of non-Q wave myocardial infarction.

LIST OF FIGURES

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FIGURE

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